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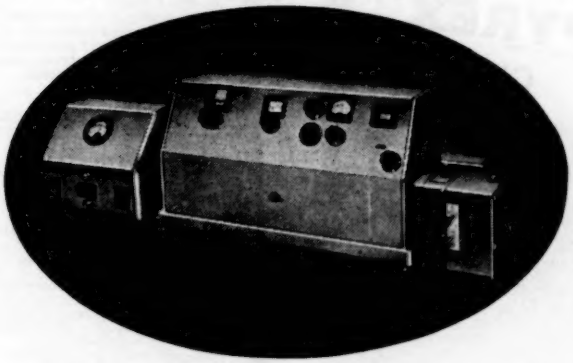

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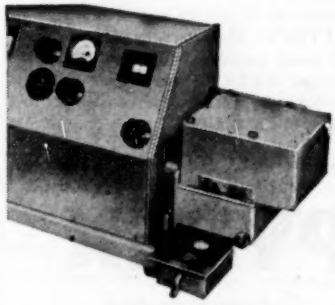

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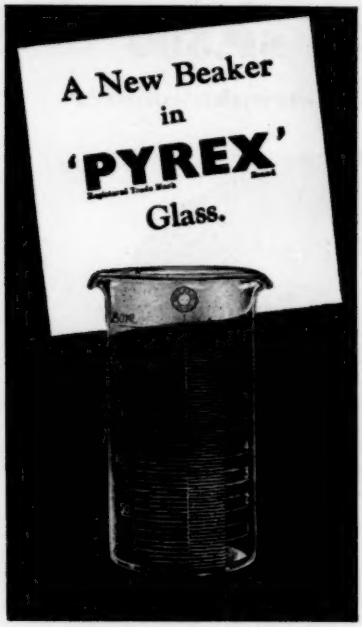

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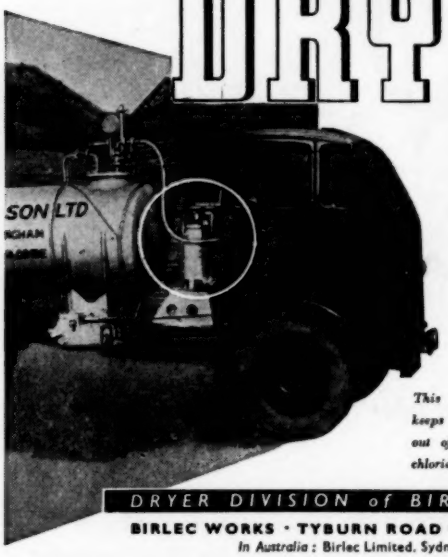

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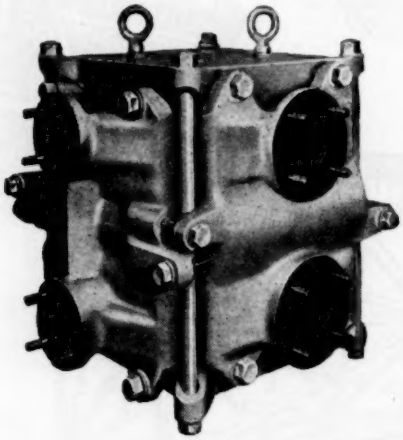

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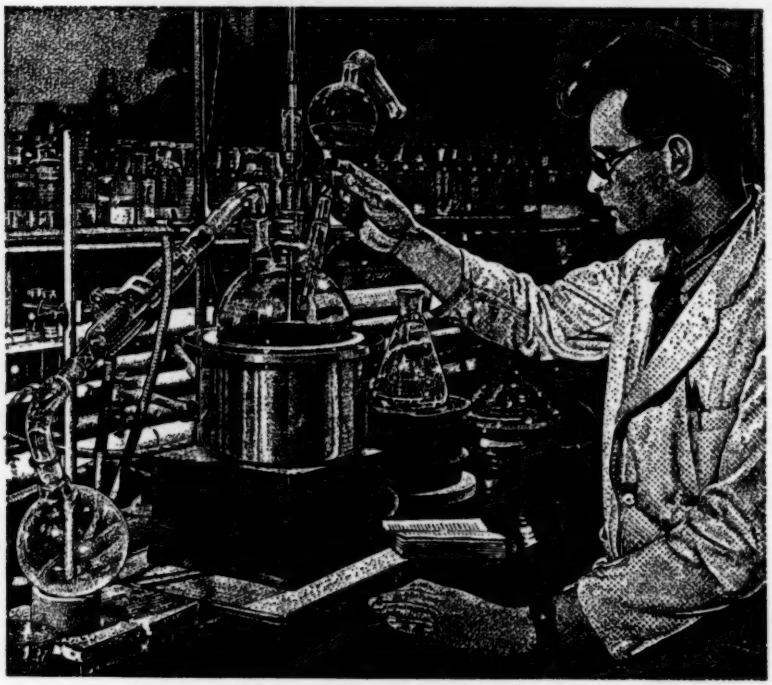

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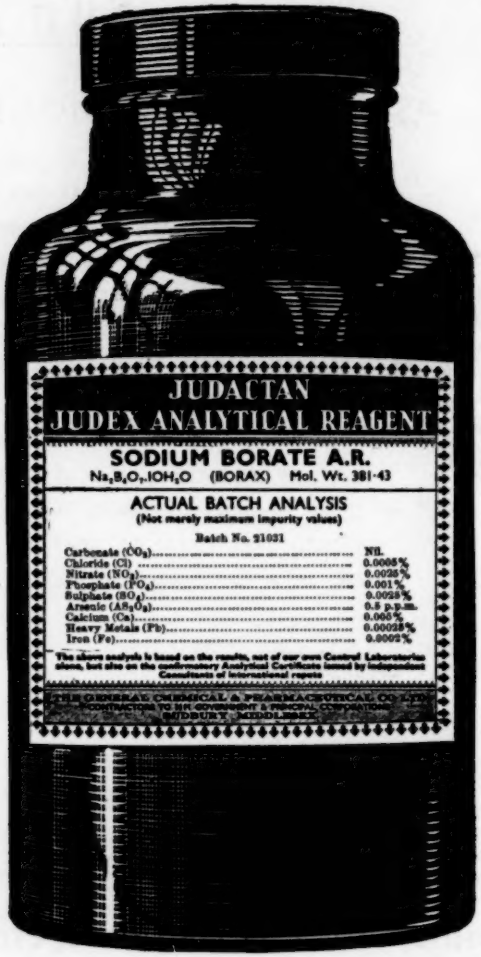

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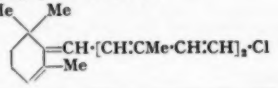
1950	3324	11 *	*for* J., 1949, 337 *read* J., 1949, 3337.
1951	1771	22	*for* Curve iv *read* Fig. 3.
	1809	4 *	for 7-7'-*methoxyindolylmethylenehydantoin* read 5-7'-*methoxyindolylmethylenehydantoin*.
	1854	1 *	*for* methyl *read* dimethyl.
	1855	7	*for* 0·000125 *read* 0·00125.
	2420	5 *	*for* (IV; R = Ph) *read* (V; R = Ph).
	2422	4	*for* Hanby, Whaley, and Watson *read* Waley and Watson.
	2738	1 *	*for* base *read* bare.
	2739		Table II, seventh column heading *for* $10^5[HOI^+]$ *read* $10^5[H_2OI^+]$.
	3002		Around formula (IV) transpose (*A*) and (*B*).
	3029		In five of the formulæ on this page *for* Pr^i *read* Pr.
	3256		Formula (IX) *should read*



* From bottom.

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The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

Fellowship of the Society is open to men and women of all nationalities who are interested in chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

PRIVILEGES

Fellows who pay the annual subscription of £3 10*s*. have the following privileges.

1. To receive a selection of the Society's publications. Publications in excess of those allowed under the Annual Subscription may be purchased at favourable rates.

   Details are available on application to the General Secretary.
2. To consult and borrow the books in the Library.
3. To attend meetings of the Society both in London and outside London, and to introduce two guests thereto.
4. To apply for research grants.
5. To submit original papers for publication in the *Journal*.

Fellows under the age of 25, who so wish, may pay an annual subscription of £1 15*s*. and enjoy all the privileges accorded to those paying the full subscription except that the choice of publications is limited.

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(*a*) *The Journal of the Chemical Society*, which is published monthly, contains the results of investigations which cover the whole field of pure chemistry.

(*b*) *British Abstracts*.—The Society collaborates with the Society of Chemical Industry, the Physiological Society, the Biochemical Society, and other organisations in contributing to the maintenance of the Bureau of Abstracts, which issues every month abstracts of papers dealing with all branches of pure and applied chemistry, physiology, and anatomy published in all parts of the world.

British Abstracts A is divided into three sections: AI, General, Physical, and Inorganic Chemistry; AII, Organic Chemistry; AIII, Physiology and Biochemistry, including Anatomy.

(*c*) *Annual Reports on the Progress of Chemistry*.—These reports, written by experts, summarise the important new advances in pure chemistry and related subjects.

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The extensive reference and lending library of the Chemical Society contains over 47,000 volumes dealing with every aspect of chemistry and with many branches of related sciences. The library is open on Monday to Friday from 10 a.m. to 9 p.m., and on Saturdays from 10 a.m. to 5 p.m.

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(*b*) *Outside London*.—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

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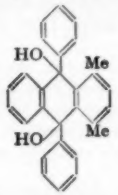
A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

Forms of Application for Fellowship can be obtained from THE GENERAL SECRETARY, THE CHEMICAL SOCIETY, BURLINGTON HOUSE, PICCADILLY, LONDON, W.1.

721. *Aromatic Hydrocarbons. Part LXII.** 1 : 2-3 : 4-9 : 10-*Tribenzopyrene.*

By E. Clar and J. R. Holker.

1 : 2-3 : 4-9 : 10-Tribenzopyrene (II) was obtained from 9 : 10-dihydro-9 : 10-dihydroxy-1 : 4-dimethyl-9 : 10-diphenylanthracene (I) by the action of copper powder at *ca.* 400°.

(I) 

(II)

Experimental.—M. p.s are uncorrected and were taken in evacuated capillaries. Microanalyses were done by Drs. Weiler and Strauss, Oxford.

9 : 10-*Dihydro*-9 : 10-*dihydroxy*-1 : 4-*dimethyl*-9 : 10-*diphenylanthracene.* The Grignard reaction, following Scholl and Meyer (*Annalen*, 1934, **512**, 112), gave a 39% yield of this diol as colourless needles (m. p. 219—220°; lit., m. p. 221—222°). Use of phenyl-lithium gives a higher-melting isomer. To a solution of phenyl-lithium from lithium chips (2·7 g.) in ether (100 c.c.) and bromobenzene (32 g.) in ether (100 c.c.), 1 : 4-dimethylanthraquinone (20 g.) was added in portions, and the solution was refluxed for 30 minutes. After decomposition of the mixture, the ether was distilled off and the residue extracted with alkaline dithionite (hydrosulphite). The yield of product was 28 g. and the m. p. 215—245° (decomp.). Extraction with boiling alcohol (150 c.c.) left a residue (17·5 g.) of m. p. 254—258°, raised by further extraction with benzene to 259—262°. Crystallisation from xylene lowered the m. p. to 213—215°. The diol, m. p. 259—262°, and the diol, m. p. 221°, both gave only 1 : 4-dimethyl-9 : 10-diphenylanthracene (Dufraisse and Horclois, *Bull. Soc. chim.*, 1936, **3**, 1900) on reduction with potassium iodide and sodium hypophosphite in acetic acid.

1 : 2-3 : 4-9 : 10-*Tribenzopyrene.*—The diol, m. p. 221° (2 g.), and copper powder (0·2 g.) were heated at 400° in carbon dioxide for 3 hours. Extraction with benzene, concentration, and dilution with light petroleum yielded a gum which was removed. Concentration of the mother-liquor to a very small volume and cooling gave an orange-yellow powder, which on recrystallisation from very little benzene yielded 25 mg. of 1 : 2-3 : 4-9 : 10-*tribenzopyrene*, m. p. 236—238°. Similar treatment of the diol, m. p. 254—258 (10 g.), followed by distillation (320°/2 mm.), gave small orange plates, m. p. 238° (175 mg.), from benzene (Found: C, 94·7; H, 4·6. $C_{28}H_{16}$ requires C, 95·4; H, 4·6%). The hydrocarbon showed a green fluorescence in organic solvents and gave a green solution in sulphuric acid, becoming brown on storage.

University of Glasgow. [*Received, July 13th*, 1951.]

* Part LXI, *J.*, 3215.

OBITUARY NOTICE.

JOSEPH HENRY LANE.

1883—1951.

JOSEPH HENRY LANE was born in London in 1883. He received his early education at Raine's School, Stepney, and his scientific training at Finsbury Technical College under Professor Raphael Meldola and Frederick William Streatfeild. After graduation he remained at Finsbury for a time as research assistant to Professor Meldola and in 1903 and 1904 collaborated in two papers, on the isomeric aminoamidines of the naphthalene series, that were published in the *Journal*.

In 1904 he accepted an appointment in the laboratory of the Beet Sugar Association, subsequently to become the Sugar Association of London, and entered upon what was to become his main interest in life. In the laboratory of the Sugar Association he met Mr. Lewis Eynon, with whom, on the closing of the Sugar Association's laboratory in 1910, he entered into partnership as a consulting chemist, specialising in the analysis of sugars and in the chemistry of fermentation.

He was admitted to Fellowship of the Society in 1941, and was a Fellow of the Royal Institute of Chemistry.

Between the years 1909 and 1931 his published work included eight papers and two monographs.

Of his published work the most important was the paper on methylene blue as an internal indicator in the volumetric determination of the reducing sugars by Fehling's solution. His collaborator in this work, Mr. Lewis Eynon, has placed it upon record in *The Analyst* that Lane played the principal part in this discovery, but many laborious months were spent by the partners in experimental verification of its accuracy and precision and in the preparation of the series of factorial tables for the various reducing sugars, which have remained in use to the present time.

According to Lane's own account, he and his partner had already spent much time in trying to improve upon the unsatisfactory external indicators, such as potassium ferrocyanide, ferrous thiocyanate, and a mixture of potassium iodide and starch, then in use; and as he stood one day in his laboratory, surrounded by numerous samples on which determinations of reducing sugars were required to greater accuracy than could be attained otherwise than by the laborious and lengthy gravimetric method, he wondered if he could find a dye that would act in a sugar titration like some of those that were just then coming into use as oxidation–reduction indicators. So he examined his collection of reagents and seeing a bottle of methylene-blue, he tried it—with the result that we all know to-day.

The methylene-blue method immediately gained world-wide recognition. C. L. Hinton wrote of it in 1930 (" Recent Advances in Analytical Chemistry," Ed. C. Ainsworth Mitchell, J. & A. Churchill, London, 1930) : " The introduction by Lane and Eynon of methylene-blue as an internal indicator was an advance of the first order. So great has been the gain, in fact, that R. F. Jackson recently stated (*J. Assoc. Off. Agric. Chem.*, 1929, **12**, 166) that ' the method is, on account of its convenience, accuracy, and rapidity, largely displacing the gravimetric methods for reducing sugar '." Hinton's statement is as true to-day as when it was first made, twenty years ago. There are not many analytical methods that have stood the test of time so well.

Lane was for many years an abstractor for *J. Soc. Chem. Ind.* and *J. Inst. Brewing*. This brought him a wide experience of the literature of analytical chemistry, which, combined with his ability to write clear, concise English, he turned to good account when he was appointed Assistant Editor to *The Analyst* (in succession to T. H. Pope) in 1936 and Editor in 1945, on the retirement of Dr. Charles Ainsworth Mitchell. He succeeded Mitchell as Secretary of the Society of Public Analysts and Other Analytical Chemists in 1937.

Lane was of a kindly, cheerful, and generous disposition, ever ready to place his knowledge and experience, freely and in full, at the disposal of others. Time and trouble counted for nothing where he could be of help.

" Good temper triumphed in his face,
And in his heart he found a place
For all the erring human race . . ."

During his last year of life he bore increasing bodily weakness with great fortitude and remained cheerful to the end, which came to him at Taplow on the 9th March, 1951.

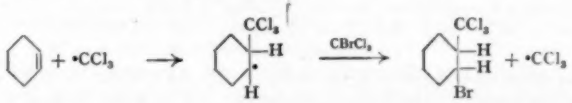
F. L. OKELL.

722. *The Reactivity of the α-Methylenic Carbon Atom of* cyclo-*Hexene in Peroxide-catalysed Radical Reactions.*

By Shalom Israelashvili and Joseph Shabatay.

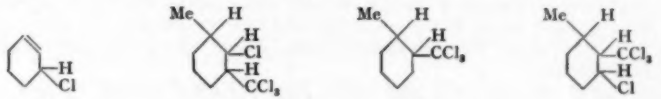
Two opposing mechanisms have been proposed for interaction of olefins with radicals: (*a*) abstraction of hydrogen from the α-methylenic carbon atom, followed by allylic substitution; (*b*) the Kharasch addition of radicals to the double bond. Investigation of the reaction of *cyclo*hexene with carbon tetrachloride, catalysed by benzoyl and acetyl peroxides, shows that both mechanisms operate simultaneously, and that reaction (*b*) occurs only with big radicals, which are excluded from allylic substitution by steric interference.

It has been shown by Farmer and Sundralingam (*J.*, 1942, 121), Farmer and Michael (*ibid.*, p. 513), Hermans and Van Eyk (*J. Polymer Sci.*, 1946, **1**, 407), Criegee (*Ber.*, 1939, **72**, 1799), Hock and Ganicke (*ibid.*, 1938, **71**, 1430), Waters (*Nature*, 1944, **154**, 772), and Ziegler *et al.* (*Annalen*, 1942, **551**, 80) that in *cyclo*hexene there are two possible sites for attack by radicals: the double bond, and the allylic carbon atom. Kharasch and Friedlander (*J. Org. Chem.*, 1949, **14**, 239, 538), however, formulated the addition of halogenated free methyl radicals, *e.g.*, trichloromethyl, to *cyclo*hexene as a chain reaction, thus:



It is not clear why these two types of free-radical reactions should follow different mechanisms, and it seemed desirable to study the reactions of *cyclo*hexene with radicals more thoroughly in order to find reasons for the two alternative courses under different conditions. We now report a study of the reaction between *cyclo*hexene and carbon tetrachloride as catalysed (*a*) by benzoyl peroxide and (*b*) by acetyl peroxide.

From the complex mixture of products obtained from *cyclo*hexene, carbon tetrachloride, and benzoyl peroxide, an approximately 10% yield of the expected 1 : 1-addition product was isolated. Its structure was proved by conversion through acid hydrolysis into *cyclo*hex-1-ene-1-carboxylic acid. A second product was formulated as $C_{19}H_{24}O_2Cl_2$ in view of its analysis and of the quantitative yield of 1 mol. of benzoic acid on alkaline hydrolysis, but its structure has not yet been conclusively established. From the volatile portion obtained in the fore-run of the distillation, a third product, 3-chloro*cyclo*hex-1-ene (I) was isolated.



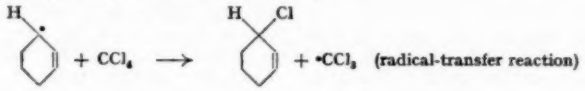
(I) (II) (III) (IV)

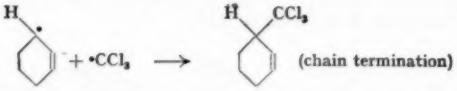
From the interaction of *cyclo*hexene, carbon tetrachloride, and acetyl peroxide, a still more complex mixture was obtained. The products not only contained the elements of carbon tetrachloride, but in some of them an additional carbon atom was introduced as a methyl group. The following products have been identified: 3-chloro*cyclo*hex-1-ene (I), 2-chloro-1-methyl-3-trichloromethyl*cyclo*hexane (II), 1-methyl-2-trichloromethyl*cyclo*hexane (III), and 3-chloro-1-methyl-2-trichloromethyl*cyclo*hexane (IV). The chloro*cyclo*hexene (I) was identified by comparison of its properties with the compound obtained by Ziegler (*loc. cit.*) from *cyclo*hexene and *N*-chlorophthalimide, and also by its conversion into 3-acetoxy*cyclo*hex-1-ene. The other compounds (II, III, and IV) were hydrolysed to the corresponding carboxylic acids by 70% sulphuric acid. Compound (III) was thus converted into *trans*-2-methyl*cyclo*hexanecarboxylic acid, and (II) and (IV) into 3-methyl- and 6-methyl-*cyclo*hex-1-ene-1-carboxylic acid, respectively.

The different results obtained in the two reactions studied may be explained on the basis of the different reactivity of the peroxide catalysts used and the stability of the radicals produced from them. Benzoyl peroxide decomposes slowly, and the small amount of primary phenyl radicals supplied will react preferentially with solvent. Acetyl peroxide is applied in double the concentration and is readily decomposed, so that a relatively high concentration of methyl radicals is formed within a short time. Apart from this difference, the reaction mechanisms are similar. In the benzoyl peroxide-catalysed reaction, the trichloromethyl radical could abstract the hydrogen atom from the α-methylenic carbon atom—analogously to the allylic substitutions mentioned before—and thus produce the *cyclo*hexenyl radical (plus chloroform) (see Kooijman, *Rec. Trav. chim.*, **1950**, **69**, 492) :

(1)

The radical thus obtained may then be stabilised in two ways :

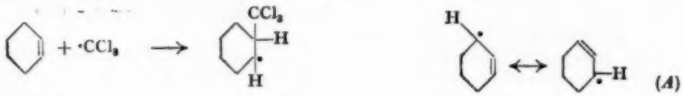
(2) 

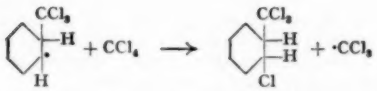
(3) 

Reaction (3) has never been observed by us to occur with the trichloromethyl radical.

In addition, the simple 1 : 1-adduct corresponding to Kharasch's scheme was obtained, and this reaction may be represented thus :

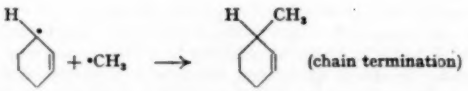
(4)

(5) 

(6) 

In the acetyl peroxide-catalysed reaction we may again assume the *cyclo*hexenyl radical to be the first intermediate, owing to the stabilising effect of resonance in the allylic radical, as in (*A*). As formed above, the *cyclo*hexenyl radical should then give 3-chloro*cyclo*hex-1-ene, which was again isolated.

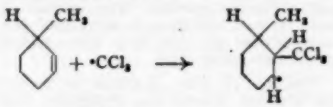
The *cyclo*hexenyl radical could also react with a methyl radical to give 3-methyl-*cyclo*hex-1-ene :

(7) 

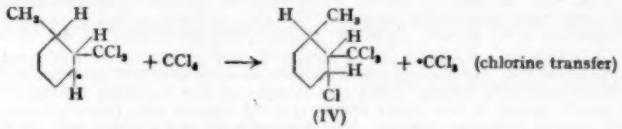
So far this derivative has not been detected among the reaction products, probably owing to the difficulty of its separation from *cyclo*hexene.

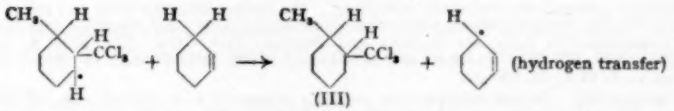
The double bond in 3-methyl*cyclo*hex-1-ene is much more susceptible to the peroxide-catalysed addition reaction of carbon tetrachloride than is the double bond in *cyclo*hexene, so one would expect that 3-methyl*cyclo*hex-1-ene would first add a radical in position 1. However, the yield of (IV) is much larger than that of (II), which shows that the trichloromethyl

radical adds abnormally (in view of the mode of radical addition to propylene) mainly in one direction, *viz.*, ortho- to the methyl group :

(8) 

This intermediate radical can either react with carbon tetrachloride to yield (IV) or abstract hydrogen from *cyclo*hexene to give (III) :

(9) 

(10) 

Although we are still far from a complete picture of the reactions involved, this investigation yields one clear result : both free-radical mechanisms are operative with *cyclo*hexene, *viz.*, allylic substitution and addition to the double bond. However, it is clear that only certain radicals can effect the substitution reaction.

In view of these considerations, the question arises why reaction (5) take place at all. Tentatively, it can be assumed that in the molecule of *cyclo*hexene it is not possible for the trichloromethyl radical to approach the α-methylenic carbon atom closely enough, whereas the much smaller methyl radical can more easily be attached there. On the other hand, the double bond in *cyclo*hexene leaves much more space for the approach of bigger radicals, and therefore the Kharasch mechanism is operative for such groups as trichloromethyl and tribromomethyl. Thus, although the allylic radical is always more stable than the secondary radical produced by addition of a radical to the double bond, steric factors prevent the substitution reactions from occurring with big radicals like trichloromethyl and thus switch the reaction mechanism from substitution to addition.

In *cyclo*hexene both ethylenic carbon atoms are equally substituted. In open-chain olefins like oct-1-ene, carbon atom 1 is much less hindered for the combination with free radicals than carbon atom 2. In addition, the inductive effect of the aliphatic substituent at carbon atom 2 polarises the double bond in such a way that a higher electron density is produced at carbon atom 1; therefore the electron-deficient radical $\cdot CCl_3$ attaches itself to the terminal carbon atom 1 (see Flory and Lautner, *J. Polymer Sci.*, 1948, **3**, 880). The approach of a big radical like trichloromethyl to the allylic position of oct-1-ene is also sterically hindered, although much less than in *cyclo*hexene. In any case our results with *cyclo*hexene indicate that even in the case of oct-1-ene the Kharasch reaction should produce partial substitution products, analogous to chloro*cyclo*hexene and to the allylic substitution product found by Bateman and Cunneen (*J.*, 1950, 941) in the reaction of oct-1-ene with *N*-bromosuccinimide.

Experimental.

M.p.s and b. p.s are uncorrected. Most of the microanalyses are by Drs. Weiler and Strauss, of Oxford.

Materials.—*cyclo*Hexene was distilled several times in a Vigreux column; it had b. p. 81°/690 mm., n_D^{20} 1·4450. Acetyl peroxide was prepared according to Gamberian's method (*Ber.*, 1909, **42**, 4010), but carbon tetrachloride was used as a solvent instead of ether. The concentration of the peroxide solution was determined iodometrically (Kokatnur and Jelling, *J. Amer. Chem. Soc.*, 1941, **63**, 1432). Commercial benzoyl peroxide was recrystallised from a small amount of warm chloroform, and had m. p. 104°.

Reaction between cyclo*Hexene and Carbon Tetrachloride in the Presence of Benzoyl Peroxide.*—In a three-necked flask fitted with a reflux condenser, a dropping funnel, a gas-inlet tube, and a thermometer, a mixture of *cyclo*hexene (41 g., 0·5 mole) and carbon tetrachloride (385 g., 2·5 moles) was refluxed for 18 hours under a continuous stream of dry carbon dioxide. At the beginning and also 9 hours

later, benzoyl peroxide (2·4 g., 0·01 mole) was added. The mixture boiled initially at 78°, and after 18 hours at 82°. The yellow solution was washed three times with a 5% solution of sodium hydrogen carbonate and with water, and dried (Na_2SO_4). The low-boiling components of the reaction mixture were removed by distillation through a Vigreux column. The residual oil was fractionated *in vacuo*, the following fractions being isolated: (i) b. p. 60°/30 mm., n_D^{20} 1·4850 (3·0 g.), a colourless liquid (I); (ii) b. p. 95—100°/10 mm. (6 g.), a colourless oil; (iii) b. p. 150—155°/10 mm. (4 g.), a yellow oil; and (iv) undistillable residue, a viscous brown syrup (1 g.).

Identification of the products. Fraction (i) was identified as 3-chloro*cyclo*hex-1-ene. Fraction (ii) was found by bromate–bromide titration (Lucas and Pressman, *Ind. Eng. Chem., Anal.*, 1938, **10**, 140) to contain a small amount of olefin. It was purified by addition of the calculated amount of bromine in chloroform. The mixture was kept in the dark for 2 hours, washed with sodium hydrogen carbonate solution, and dried, and the chloroform residue distilled *in vacuo*. A colourless oil was obtained, b. p. 98—100°/10 mm., n_D^{20} 1·5232. The *product*, as indicated by analysis and by titration as before, still contained some unsaturated material (? $C_7H_9Cl_3$), probably formed by decomposition during distillation (Found: C, 37·0; H, 4·8; Cl, 58·55. $C_7H_{10}Cl_4$ requires C, 36·1; H, 4·3; Cl, 59·6%).

Acid hydrolysis of fraction (ii). Fraction (ii) (0·37 g.) was added to 70% sulphuric acid (15 c.c.), with vigorous stirring, and the mixture warmed in an oil-bath at 100° for 5 hours. The yellow solution first obtained gradually became brown and strongly evolved hydrogen chloride. The solution was cooled, an equal volume of cold water added, and the organic acid extracted from the ethereal layer with 10% sodium carbonate solution. The aqueous layer was acidified with dilute sulphuric acid, and the precipitate obtained was extracted with ether. The residue from the ether was left in an ice-box overnight. Yellow crystals (100 mg.) were thus obtained, m. p. 38—39° (identical with the value for *cyclo*hex-1-enecarboxylic acid; see Ruzicka and Brugger, *Helv. Chim. Acta*, 1926, **9**, 402; Berlingozzi, *Gazzetta*, 1927, **57**, 255; Boorman and Linstead, *J.*, 1935, 261) (Found: C 66·2; H 7·8. Calc. for $C_7H_{10}O_2$: C, 66·6; H, 7·9%).

Fraction (iii). On redistillation, this yielded a yellow oil, b. p. 155°/10 mm., n_D^{20} 1·5387, which was olefinic [Found: C, 63·3; H, 6·6; Cl, 19·5%; *M* (Rast), 350. $C_{10}H_{14}O_2Cl_2$ requires C, 64·2; H, 6·8; Cl, 20·0; *M*, 355] (Bromine titration: 1 g. absorbed 410 mg. Calc.: 450 mg.).

Alkaline hydrolysis of fraction (iii). Fraction (iii) (0·3 g.) in alcoholic 0·5N-sodium hydroxide (25 c.c.) was refluxed for 2 hours. Distilled water was added (25 c.c.), and a titration carried out with 0·5N-hydrochloric acid (phenolphthalein): 97·44 mg. of alkali were consumed, equivalent to 3 moles per mole of fraction (iii) if it has *M*, 355. The solution obtained after the titration was evaporated to dryness on a water-bath, and the residue extracted with a solution of sodium hydrogen carbonate. About one-third of it dissolved. The aqueous layer was acidified with dilute sulphuric acid. The precipitate (100 mg.), recrystallised from water, yielded colourless crystals, m. p. 120° (mixed m. p. with benzoic acid, 120°). The remainder was dissolved in ether, the solution filtered, the solvent removed, and the residue triturated with ligroin. Colourless crystals, m. p. 52°, were obtained. These had a camphor-like smell, but after 24 hours in an open vessel they had almost completely evaporated.

Reaction between cyclo*Hexene and Carbon Tetrachloride in the Presence of Acetyl Peroxide.*—A mixture of *cyclo*hexene (82 g., 1 mole), carbon tetrachloride (708 g., 5 moles), and acetyl peroxide (0·4 g.) was refluxed in a continuous stream of carbon dioxide. At intervals of 6 hours additional portions of acetyl peroxide were added (total 2·4 g., 0·04 mole). The b. p. initially was 78°, and after 30 hours 86°. After purification of the product as described above, the reagents were removed by distillation, and the residue (36 g.) distilled *in vacuo*. A fore-run was lost owing to its low b. p. The following fractions were obtained: (i) b. p. 50—55°/20 mm., n_D^{26} 1·4853, d_4^{20} 1·028 (3·0 g.), a colourless liquid (I); (ii) b. p. 105—110°/18 mm., n_D^{20} 1·5014 (1·5 g.), a colourless oil; (iii) b. p. 112—114°/18 mm., n_D^{20} 1·5167 (1·5 g.), a yellow oil; (iv) b. p. 120°/18 mm., n_D^{20} 1·5197, d_4^{20} 1·299 (5 g.) (III), a yellow oil; (v) b. p. 160°/18 mm., n_D^{20} 1·5094 (a very small amount), a yellow oil; (vi) b. p. 120°/5 mm., n_D^{20} 1·5217, d_4^{20} 1·367 (7 g.) (II and IV), a yellow oil.

Identification of the fractions. Fraction (i) was identified as 3-chloro*cyclo*hex-1-ene as follows. It (Found: C, 61·4; H, 8·1; Cl, 30·7. Calc. for C_6H_9Cl: C, 61·8; H, 7·8; Cl, 30·4%) rapidly formed a precipitate with alcoholic silver nitrate; titration with bromate–bromide showed the existence of one double bond; comparison of the above physical data showed good agreement with those given by Berland (*Bull. Soc. chim.*, 1942, **9**, 644), *viz.*, b. p. 62°/35 mm.; n_D^{20} 1·4860; d_D^{20} 1·030.

Conversion of 3-*chloro*cyclo*hex*-1-*ene into* 3-*acetoxy*cyclo*hex*-1-*ene.* A mixture of fraction (i) (0·2 g.), anhydrous sodium acetate (0·25 g.), and glacial acetic acid (5 c.c.) was kept for 24 hours at room temperature, then extracted with ether; the extract was washed with water and a solution of 5% sodium hydrogen carbonate, and dried (Na_2SO_4). Evaporation of the ether left a small quantity of viscous, yellow oil. The 3-acetoxy*cyclo*hexene so obtained showed physical constants corresponding to those given by Berland (*loc. cit.*): b. p. 83—84°/30 mm., d^{25} 1·003, n_D^{20} 1·4580 (Found: C, 68·8; H, 8·3. Calc. for $C_8H_{12}O_2$: C, 68·5; H, 8·5%).

Fraction (iv). This was identified as 1-*methyl*-2-*trichloromethyl*cyclo*hexane* (III) by analysis (Found: C, 44·9; H, 5·75; Cl, 49·1%; *M*, 218. $C_8H_{13}Cl_3$ requires C, 44·6; H, 6·0; Cl, 49·3%; *M*, 213) ($[R_L]_D$ 50·36. Calc.: 50·54), and by acid hydrolysis to 2-methyl*cyclo*hexanecarboxylic acid by the method described above. Yellow crystals, m. p. 52—54°, were obtained (cf. Goldschmidt, *Chem.-Ztg.*, 1902, **26**, 335; Gutt, *Ber.*, 1907, **40**, 2069) (Found: C, 67·3; H, 10·2%; equiv., 142·5. Calc. for $C_8H_{14}O_2$: C, 67·6; H, 9·9%; equiv., 142·0).

Fraction (vi). This fraction, which constituted about 40% of the total products of the reaction, is believed to be a mixture of (II) and (IV) (Found: C, 38·1; H, 4·85; Cl, 57·0%; *M*, 260. Calc. for $C_8H_{12}Cl_4$: C, 38·4; H, 4·8; Cl, 56·8%; *M*, 250) ($[R_L]_D$ 56·85. Calc.: 56·77); it was completely saturated towards perbenzoic acid and bromine.

Hydrolysis of fraction (vi). Fraction (vi) (1 g.) was added to 70% sulphuric acid (10 c.c.), with stirring,

and the whole warmed on a steam-bath for 3 hours. The red solution first obtained became brown and evolved hydrogen chloride. It was then poured on chopped ice and extracted with ether, and the solvent removed. The residue was dissolved in carbon tetrachloride and chromatographed on activated silica gel (100 mesh). Two zones were obtained, which were separated by elution with ether–ethanol (1 : 1). After removal of the solvent from the separate percolates, the two products were isolated : (i) crystalline 6-methyl*cyclo*hex-1-ene-1-carboxylic acid (0·3 g.), m. p. 79° (cf. Mazza and Cremona, *Gazzetta*, 1927, **57**, 318) (Found : C, 68·2; H, 8·8%; equiv., 141. Calc. for $C_8H_{12}O_2$: C, 68·5; H, 8·5%; equiv., 140); (ii) a yellow oil which crystallised at 25° (100 mg.), identical with 3-methyl*cyclo*hex-1-ene-1-carboxylic acid (see Perkin and Tattersall, *J.*, 1905, **87**, 1095; Boorman and Linstead, *J.*, 1935, 264) (Found : C, 68·7; H, 8·6%; equiv., 139·2).

Fractions (ii) (Found : C, 54·7; H, 7·8; Cl, 30·55%), (3) (Found : C, 47·8; H, 6·1; Cl, 40·0%), and (v) (Found : C, 53·6; H, 6·9; Cl, 39·15%) are being investigated further. Fraction (v) represented 5% of the total reaction products.

The authors thank Professor Felix Bergmann for discussions on this subject and for help in preparing the manuscript.

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723. *Some Free-radical Reactions of Phenol. The Action of the Hydrogen Peroxide–Ferrous Salt Reagent and of X-Rays on Aqueous Solutions of Phenol.*

By GABRIEL STEIN and JOSEPH WEISS.

The action of OH and HO_2 radicals, produced by Fenton's reagent and irradiation with *X*-rays, respectively, on phenol in aqueous solution has been studied as a sequel to that on other benzene derivatives. Only the *o*- and the *p*-dihydroxy-derivative are formed, their relative ratios depending on the pH.

The mode of action of Fenton's reagent has been reinvestigated, with special reference to the role of the ferric ions in this system.

Under certain experimental conditions quinonoid products, and in particular *o*-benzoquinone, may be formed, apparently without the intermediate formation of quinol or catechol. This quinone obtained in *acid* solution has been shown to be similar to that obtained by the action of the enzyme tyrosinase on phenol in *neutral* solutions. Possible reaction mechanisms have been outlined.

A method for the determination of small quantities of catechol and quinol, in the presence of a large excess of phenol, and a colour reaction for *o*-benzoquinone, are described.

Further experiments on the action of mixed γ-ray–neutron radiations on benzene and on phenol under various conditions are reported.

IN previous papers we have shown that free OH radicals can hydroxylate aromatic compounds. The radicals were produced by the hydrogen peroxide–ferrous salt (Fenton's) reagent and also by the action of ionising radiations on aqueous solutions (Stein and Weiss, *Nature*, 1950, **166**, 1104). The products were similar in the two cases, and it has been shown that nitrobenzene gives the isomeric nitrophenols in relative proportions which are identical within the limits of experimental error (Loebl, Stein, and Weiss, *J.*, 1949, 2074; 1950, 2704; see also *J.*, 1951, 405).

The use of the radiations to form the radicals is sometimes preferable to that of Fenton's reagent, since in the former case secondary reactions due to the metal ions are avoided and a much wider range of pH can be used. Also, Fenton's reagent can lead to a chain reaction which is often difficult to reproduce exactly, whereas when *X*-rays are used the amount of radicals formed is known and easily controlled.

We have now investigated the action of these radicals on phenol. Both the nitro- and carboxy-groups present in the compounds investigated previously (Loebl, Stein, and Weiss, *loc. cit.*) are *meta*-directing, whilst the hydroxy-group is *ortho–para*-directing. It was of interest to investigate the influence of this on substitution by a free radical (cf. Stein and Weiss, *Nature*, 1950, *loc. cit.*).

The action of Fenton's reagent on phenol has been studied previously by Martinon (*Bull. Soc. chim.*, 1885, **43**, 156) and by Goldhammer (*Biochem. Z.*, 1927, **189**, 85) amongst others.

In the classical work of Wieland and Franke (*Annalen*, 1927, **457**, 1; 1929, **475**, 1), this system served as a prototype of heavy-metal enzyme systems. Fichter and Stocker (*Ber.*, 1914, **47**, 2014; cf. Fichter and Brunner, *Bull. Soc. chim.*, 1916, **19**, 281) studied the electrolytic oxidation of phenol. Williams ("Detoxication Mechanisms," Chapman and Hall, 1947) summarised the previous work on the metabolism of phenol, and later (Porteous and Williams, *Biochem. J.*, 1949, **44**, 46, 56; Garton and Williams, *ibid.*, p. 234; 1949, **45**, 158) reinvestigated this problem. In all these cases it was found that the *meta*-isomer, resorcinol, was apparently not formed at all. However, side reactions and secondary processes made a quantitative investigation of the substitution ratios rather difficult. Baernstein (*J. Biol. Chem.*, 1945, **161**, 685), in a recent re-investigation of the biological oxidation of phenol, developed an analytical method for relatively small quantities of the hydroxylation products and has confirmed the formation of quinol and catechol. On the other hand, predominantly resorcinol was found in Barth's early work on the sodium hydroxide fusion of phenol, confirmed later by Lemberg (*Ber.*, 1929, **62**, 592), who produced evidence that this reaction presumably proceeds by way of a dehydrogenation mechanism, even in the absence of oxygen.

The Action of Fenton's Reagent.—With Fenton's reagent the conditions are somewhat complex (cf. Wieland, *loc. cit.*). The Fe^{3+} ions produced form complexes with the phenols, whilst the ferrous–ferric system enters into oxidation–reduction processes with the products. In this way some ferric iron can be again reduced to the ferrous state, thus contributing to the stationary ferrous-ion concentration in the solution. Repeating the work of previous workers, we have confirmed their results, and found that with this system reproducible results were particularly difficult to obtain. Even under conditions which led to a moderate reaction with nitrobenzene, phenol reacted violently and secondary processes, including quinone formation, obscured the final results. The secondary reactions could, however, be inhibited by a relatively small amount of ionic fluoride or pyrophosphate. In the presence of these, or of relatively large amounts of phosphate ions, only a slow reaction occurs which can be almost completely inhibited by the use of a large excess of these anions. By choice of suitable conditions, hydroxylation of phenol can then be carried out without the formation of quinones. We thus found that quinol and catechol were formed in the approximate ratio of 3 : 1 (see Table 1), with not more than 2 parts % of resorcinol, as estimated by means of colour reactions.

The action of added fluoride or phosphate consists in the elimination of the ferric ions in solution by complex formation, thus preventing the oxidation of the dihydroxybenzenes by ferric ions. On the other hand, any quinones formed by the oxidation of the dihydroxybenzenes by radicals could be reduced by the ferrous salt which, particularly in the presence of ferric complexes, would have a strong reducing action. However, the drastic inhibition of the hydroxylation reaction itself by fluoride and pyrophosphate cannot be explained on this basis alone, and it must be assumed that complex formation by the ferric ions has influenced the mechanism of the action of Fenton's reagent itself. It seems then that the role of the ferric ion in this reaction is more important than was hitherto assumed.

We have accordingly carried out experiments with ferric salts and hydrogen peroxide and have shown that aromatic hydroxylation takes place under these conditions. Similar experiments have been published in the meantime by Andersen (*Acta Chem. Scand.*, 1950, **4**, 207). These results may have one or more of several causes. It may be that ferric ions themselves can take the place of ferrous ions in the reaction leading to the hydroxylation. On the other hand it is also possible that ferric ions are necessary only as a source of a continuous supply of ferrous ions, formed, *e.g.*, by the reduction of ferric ion by HO_2^- or O_2^- (cf. Haber and Weiss, *Proc. Roy. Soc.*, 1934, *A*, **147**, 332). In the presence of a (relatively) high concentration of ferrous ion, such as may still exist initially under ordinary conditions, these would interact: $Fe^{2+} + OH \longrightarrow Fe^{3+} + OH^-$, and could very seriously compete for the available OH radicals, especially as the concentration of the aryl radicals is comparatively low; hydroxylation will then be inhibited. The retention of the OH radical in the hydroxylation process is then of fundamental importance.

It is also possible, however, that the HO_2 radical itself is capable of dehydrogenating an aromatic compound (RH): $RH + HO_2 \longrightarrow R + H_2O_2$. In this case the ferric salt–hydrogen peroxide reagent would be genuinely capable of aromatic hydroxylation. However, this reaction is about 25 kcals. less exothermic than the corresponding reaction of the OH radical because of differences in the bond energies of H–OH and H–O_2H.

These points will be discussed in subsequent publications.

It will be seen from Table I that whenever the ferric salt formed in the reaction is not removed as complex, and especially when only ferric ions are used, the formation of catechol exceeds

that of quinol. Although Baernstein's analytical procedure (which we used) involves the reduction of any quinones formed, it is still liable to give somewhat erroneous results (perhaps owing to formation of dihydroxydiphenyls, which would interfere). It therefore remains possible that the hydroxylation process is influenced by the ferric ion, possibly reacting as the $(FeOH)^{2+}$-complex (cf. Rabinowitsch and Stockmayer, *J. Amer. Chem. Soc.*, 1942, **64**, 335; Evans, George, and Uri, *Trans. Faraday Soc.*, 1949, **45**, 230; Evans and Uri, *Nature*, 1950, **166**, 869). This might occur thus: $(FeOH)^{2+} + R \longrightarrow ROH + Fe^{2+}$. Since in a reaction with a charged complex the OH radical is only implicit, different substitution ratios could result.

In addition to the possible formation of phenol in this manner, this reaction involves also the reduction of ferric to ferrous ion by the radical which is the product of the primary reaction. Therefore this reaction may also contribute to the steady state equilibrium of ferric–ferrous ions, as indicated above.

The Action of X-*Rays in Aqueous Systems.*—The results obtained with Fenton's reagent, although of qualitative interest, gave little quantitative information. Use of ionising radiations proved superior.

TABLE I.

Reaction of Fenton's reagent with phenol.

Initial amount of phenol: 0·5 millimole in 100 ml. of solution.

Molar ratios of phenol : H_2O_2 : Fe^{2+}	Conditions	Product formed (millimoles), quinol	Product formed (millimoles), catechol	Ratio, quinol / catechol	Remarks
1 : 1 : 0·25 (Fe^{3+})	Ferric ion only	0·011	0·097	0·1	Quinones formed
1 : 0·2 : 0·05	No addition	0·017	0·047	0·36	,, ,,
1 : 0·2 : 0·05	$2·5 \times 10^{-3}$ mole of NaF added	0·047	0·016	2·9	No quinone formed
1 : 0·2 : 0·05	0·12 mole of NaF added	0	0	—	Almost complete inhibition
1 : 1 : 0·5	,, ,,	0	0	—	,, ,, ,,

TABLE II.

Action of X-*rays on phenol in aqueous solutions.*

Dose: approx. 1×10^6 E.U.; volume 100 ml. Initial concn. of phenol: 0·5 millimole/100 ml.

pH	Conditions	Products formed (millimoles), quinol	Products formed (millimoles), catechol	Ratio, quinol / catechol	pH	Conditions	Products formed (millimoles), quinol	Products formed (millimoles), catechol	Ratio, quinol / catechol
2	Air	0·034	0·008	4·2	2	Vacuum	0·033	0·007	4·7
6	,,	0·030	0·020	1·5	6	,,	0·018	0·009	2·0
12	,,	0·024	0·009	2·6	12	,,	0·028	0·007	4·0

Baernstein's analytical method was at first used. However (cf. Table II), irradiation with the relatively large total dose of $\sim 1 \times 10^6$ E.U. (300 min. at a dose rate of 3000 E.U./min.) provided a yield which was barely sufficient for analysis and, therefore, subject to a large experimental error. Moreover, as we have shown previously (*J.*, 1949, 3245; Day and Stein, *Nature*, 1949, **164**, 671) the oxygen present in water saturated with air suffices for only a dose of approx. 6×10^4 E.U., and so irradiations with much greater doses are carried out mainly in the virtual absence of oxygen. We have used also solutions saturated with oxygen at 1 atm., but even here the oxygen suffices for only a dose of approx. $2·5 \times 10^5$ E.U.

The results shown in Table II indicated a ratio quinol : catechol of 1·5—2, in approximately neutral solution, rising to higher values in acid and alkaline media. The values obtained in the latter case were similar to those obtained by the use of Fenton's reagent, in the presence of complex-forming agents and in acid solution. Again, no resorcinol was found in the irradiated solutions.

A more sensitive analytical procedure was needed for quinol and catechol, so that smaller doses of radiation could be used. The advantage of very low doses lies also in the very low conversion of the starting material, so that the probability of any secondary attack on the primary reaction products is very small, as was proved earlier when doses of the same order were applied to aqueous solutions of nitrobenzene, benzoic acid, and chlorobenzene.—However, one should note that dihydroxydiphenyls can be formed by the interaction of the primary phenol radicals with phenol or possibly also by the dimerisation of two phenol radicals (cf. Stein and Weiss, *J.*, 1949, 3245).

A method of analysis answering our requirements consisted of the determination of (*a*) catechol by a titanium salt at a closely controlled pH and (*b*) the sum of (quinol + catechol) by Folin's reagent in acid solutions where neither phenol nor 4 : 4′-dihydroxydiphenyl interfered. The accuracy of determination of catechol was ±3%, but that for quinol (determined by difference) was only ±5—10%. Five experiments were thus used to fix each point in Fig. 1. The results show that the formation of both quinol and catechol in approximately neutral solution is a linear function of the radiation dose. In these cases the ratio quinol : catechol is about 2. The presence of hydrogen peroxide in the irradiated solution would have influenced the results to some extent: it was shown, however, that solutions of phenol, irradiated at a neutral pH, contained no more than negligible amounts of hydrogen peroxide.

FIG. 1.

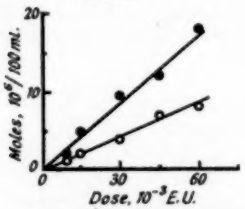


FIG. 2.

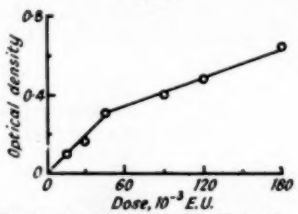


FIG. 1. *Irradiation of phenol in aqueous solution (2 millimole/100 ml.) at pH ~6. Dependence of the yield of catechol (○) and of quinol (●) on the dose.*

FIG. 2. *Irradiation of phenol in aqueous solution at pH 2·2. Dependence of quinone formation on the dose (optical density determined at λ = 290 mμ).*

FIG. 3.

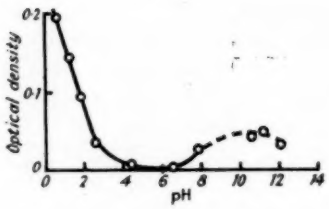


FIG. 4.

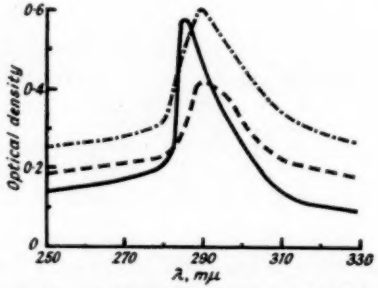


FIG. 3. *Irradiation of phenol in aqueous solution at a constant dose of approx. 6 × 10^4 E.U. Dependence of quinone formation on the* pH (*optical density determined at* 430 mμ).

FIG. 4. *Absorption spectra of irradiated phenol solutions. Dose approx. 6 × 10^4 E.U.*
———— *Irradiated at* pH 6; *spectrum determined at* pH 6.
— — — — *Irradiated at* pH 2·2; *spectrum determined at* pH 2·2.
— · — · — *Irradiated at* pH 2·2; *spectrum determined at* pH 6.

Irradiations in Acid and Alkaline Solutions.—Acid or alkaline solutions containing dissolved oxygen developed, when irradiated, a yellow or a red colour respectively. In alkaline solutions, this colour formation could not be entirely separated from the processes of autoxidation of the quinol and catechol present, which proceed readily at these pH values; nevertheless, comparison of unirradiated and irradiated alkaline samples which had been exposed to oxygen for the same length of time, showed the red colour to be due mainly to the radiation. In the acid solutions, where autoxidation does not occur, the colour was a well defined function of the radiation dosage (Fig. 2); incidentally acid solutions of phenol containing quinol and catechol remained colourless unless irradiated. The colour formed in the irradiated acid solutions could be discharged by adding sulphur dioxide to the acid or after neutralised solution; thereafter quinol and catechol were shown to be present, the ratio being about 4. Acid solutions of phenol irradiated in the absence of air remained colourless, but again the ratio was about 4.

The coloured substances are possibly quinonoid. Colour formation is strongest at the low pH values (see Fig. 3), disappears completely at pH ~4—7, and reappears again at more alkaline pH. The reappearance is genuine and occurs under conditions where autoxidation is not yet very noticeable. The experiments could not be followed, however, to higher pH values because from pH ~11 the red (quinonoid) product changes spontaneously, in a fast reaction, into another product with a different absorption spectrum (its maximum is at approx. 310 mμ and the optical density is lower at 430 mμ). The spectra of the irradiated phenol solutions are shown in Fig. 4, being obtained from the difference between the unirradiated and irradiated solutions. " Neutral " solutions of phenol (buffered or unbuffered) show, after irradiation, a spectrum in the near ultra-violet which is consistent with a mixture of quinol and catechol. Acid solutions of phenol show, after irradiation, a spectrum which indicates the presence of quinones. If an irradiated acid solution is gradually neutralised, the wave-length of maximum absorption is unchanged, but the general light absorption in-

FIG. 5.

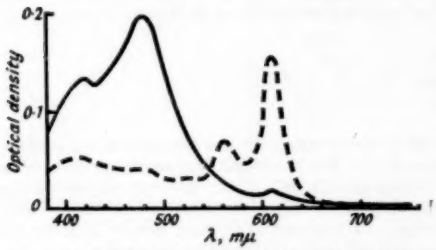


FIG. 6.

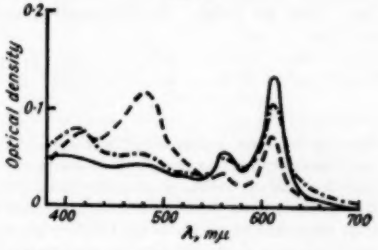


FIG. 5. *Absorption spectra of the products of reactions of* p- (————) *and of* o-*benzoquinone* (— — — —) *with* o-*phenylenediamine.*

FIG. 6. *Absorption spectra of the reaction products of* o-*phenylenediamine with* (————) *phenol solution irradiated at* pH 0·6, (— · — · —) *phenol solution treated with tyrosinase at* pH 7, *and* (— — — — —) *a solution of* p-*benzoquinone in acid, to which catechol has been added.*

creases; this increase is proportional to the pH, as shown in Table III; this behaviour is similar to that of, *e.g.*, quinhydrone or phenoquinone, but does not correspond entirely to any of the derivatives of *p*-quinone which we have tested.

TABLE III.

Dependence of optical density on pH *after irradiation.*

(Solutions of phenol irradiated at pH 1·2 with a dose of approx. 6×10^4 E.U. Results obtained with two different solutions for ascending and with one solution for descending pH. Optical density determined at ~430 mμ, Ilford filter No. 601.)

pH	Optical density (x)	10^2x/pH	pH	Optical density (x)	10^2x/pH
1·75	0·077	4·40	8·00	0·353	4·42
2·00	0·086	4·30	6·15	0·256	4·17
2·30	0·098	4·26	5·70	0·245	4·30
			5·45	0·236	4·33
2·60	0·126	4·84			
3·10	0·145	4·67			
3·85	0·174	4·52			
4·95	0·203	4·10			

Reaction with aniline (Pugh and Raper, *Biochem. J.*, 1927, **21**, 1375) gave positive results for the presence of an *o*-quinone but the yields were insufficient for isolations of solid derivatives. Following a suggestion by Dr. D. G. I. Felton we found that *o*-phenylenediamine and authentic *o*-benzoquinone in acid solution gave a brilliant green solution with an exceptionally strong red fluorescence noticeable even at approx. 0·1 micromole/ml. Solutions containing *p*-benzoquinone or its derivatives gave non-fluorescent red solutions. Fig. 5 shows the spectra of the products of reaction of *o*- and *p*-benzoquinone with *o*-phenylenediamine in acid solution.

Solutions of phenol irradiated at or below pH ~1 give, after treatment with *o*-phenylenediamine, spectra identical with those of *o*-benzoquinone (Fig. 6).

These results indicate that irradiation of acid phenol solutions gives an *o*-quinone. It is of

interest that Pugh and Raper (*loc. cit.*) found that the action of the enzyme tyrosinase on a neutral solution of phenol yields an *o*-quinone. We have repeated this experiment using tyrosinase prepared from mushrooms, and a 0·2% solution of phenol at pH ~7. After 30 minutes at room temperature the reaction mixture was acidified and treated with *o*-phenylenediamine. The spectrum of the resulting solution was identical with that of *o*-benzoquinone, or that of the irradiated phenol solution (Fig. 6).

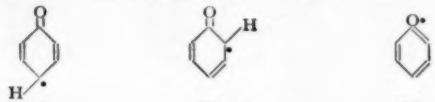
The substance present in these irradiated solutions, which thus appears to be an *o*-quinone, must co-exist with an excess of quinol (cf. Fig. 3, and results after reduction, Experimental section). The question arises whether these can be in a stable equilibrium in solution.

We find that *o*-benzoquinone does not react with quinol in acid solution : the spectrum of the product obtained by adding *o*-phenylenediamine to this mixture is identical with that obtained from *o*-benzoquinone. On the other hand, *p*-benzoquinone reacts with catechol in acid solution : the *o*-phenylenediamine test shows the presence of *o*- as well as of *p*-benzoquinone (Fig. 6). This may appear somewhat surprising, as the normal potential of *o*- is slightly higher than that of *p*-benzoquinone (by approx. 0·09 v according to Conant and Fieser, *J. Amer. Chem. Soc.*, 1924, **46**, 1858). In this system, however, one deals with the equilibrium :

The state of this equilibrium will depend not only on the standard free energies of the separate components, but also on the free-energy changes due to the corresponding quinhydrones, which may be any of three or possibly four different combinations. Thus, the free-energy change due to these may possibly exceed the small difference in the oxidation potentials of the quinones that may still exist under the conditions employed. It appears then, that in acid solutions the equilibrium is shifted towards a system in which the *o*-quinone is capable of existence.

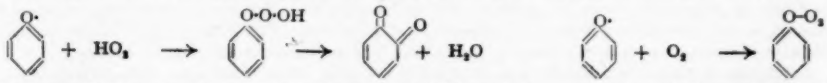
As to the mode of formation of this quinone, we have already excluded the possibility that it is the product of the autoxidation of quinol or catechol, which are primarily formed. There is also the possibility that quinol and catechol, once formed, could be further oxidised by the radiation, even in the presence of a large excess of phenol. This is unlikely, however, for the following reasons : the addition of a small quantity of quinol and catechol (such as would be formed by the irradiation) to a solution of phenol before irradiation does not increase the yield of the quinone. Also Fig. 2 shows that the formation of the quinone is linear with the dose, even at very low doses, and does not show an induction period for the formation of the diols. Fig. 3 moreover shows that in neutral solutions, where more quinol and catechol are formed and where both quinol and catechol are inherently easier to oxidise, quinone formation does not occur. Fig. 3 rather suggests that the formation of the quinone depends on some intermediate entity which is subject to a pH-dependent equilibrium.

All these results indicate that the quinone is formed not from, but in place of, quinol and catechol. The reaction may occur in the following stages: phenol is dehydrogenated by a free radical to yield the free phenol radical, which can, however, exist in several forms, *e.g.*, (*A*—*C*). Some of these forms are explicitly quinonoid (cf. Wheland, *J. Amer. Chem. Soc.*,



(*A*) (*B*) (*C*)

1942, **64**, 900) and could yield the observed quinol : catechol ratio and exclusively *ortho–para*-substitution. Structure (*C*), moreover, may result directly by dehydrogenation of phenol, and it is possible that in strongly acid solutions this point of dehydrogenation will compete with dehydrogenation in the ring. This structure may yield *o*-quinone, *e.g.*, according to the schemes :



The ozonide-like structure resulting from the addition of O_2 may lead to ring opening (Stein and Weiss, *J.*, 1949, 3254). The significance of the different mesomeric forms of the phenol

free radical has been pointed out recently by Cosgrove and Waters (*J.*, 1951, 388). Also, at different pH values different mechanisms may operate for the decomposition of the peroxide under consideration. The role of similar structures has been already considered for cresols by Pummerer, Puttfarcken, and Schopflocher (*Ber.*, 1925, **58**, 1808) and by Westerfeld (*J. Biol. Chem.*, 1942, **145**, 463). Somewhat similar considerations have been employed also by Saunders and Watson (*Biochem. J.*, 1950, **46**, 629) in describing the action of peroxidase, whilst a shift to a quinonoid structure in both acid and alkaline media is described by Witkop and Patrick (*Experientia*, 1950, **6**, 183). In our view, under the experimental conditions employed in the present work, oxidation of phenol to a quinonoid product occurs without the intermediate formation of a dihydroxybenzene.

The quinonoid product which predominated in our experiments was an *o*-quinone. The very interesting fact emerges that the free-radical oxidation of phenol, *in vitro*, at an acid pH leads to the same product as the action of tyrosinase at a *neutral* pH. The function of the acid environment in our case appears to be to ensure the stability of one particular intermediate. Similarly one role of the enzyme surface could be to stabilise one particular form of the radical by providing a suitable environment, corresponding to a lower pH.

This view is supported by the work of Kuhn and Wagner-Jauregg (*Ber.*, 1934, **67**, 361) and of Haas (*Biochem. Z.*, 1937, **290**, 291) who showed that the semiquinone radical of lactoflavine which was stable *in vitro* only in acid solutions became stable in neutral solutions on the surface of the protein, in combination with which it forms the enzyme (" yellow ferment ").

Further Experiments on the Action of Neutrons on Benzene and Phenol in Aqueous Solutions.—In previous papers (Stein and Weiss, *Nature*, 1948, **161**, 650; *J.*, 1949, 3254) we have reported some preliminary experiments with a mixed γ-ray–neutron source, with aqueous solutions of benzene in a vacuum. We found quinol and catechol, in addition to phenol. Using dinitrophenylhydrazine as a reagent, we isolated a product which appeared to be a dialdehyde formed by opening of the benzene ring. In view of the apparent connections with the present work, we have carried out some further experiments.

The only source of neutrons at our disposal was a 1-g. Ra–Be source, giving approx. 10^{10} γ-ray quanta and approx. 10^6 neutrons per second, so that only a small fraction of the energy absorbed in the irradiated solution is due to the neutrons.

Using the colour reaction described above we confirmed our earlier finding that, with a constant γ-ray intensity, the yield was approximately twice as great when the mixed radiation was used. In view of the low neutron intensity, this was remarkable; it resembles the results of Hopwood and Phillips (*Nature*, 1935, **136**, 1026; 1939, **143**, 640). If the irradiations are carried out in the presence of oxygen, this difference between the yields from γ and γ–n sources disappears (Dr. M. Ebert, personal communication; we have confirmed this result). Thus, it is possible that the cause of the difference in the experiments in a vacuum is the formation of oxygen by neutrons. If so, the effect would at least qualitatively be similar to the differential effects observed between densely and sparsely ionising radiations (Bonét-Maury and Lefort, *Nature*, 1948, **162**, 381; Haissinsky and Lefort, *Compt. rend.*, 1949, **228**, 314). Irradiating a neutral solution of phenol with *X*-rays or with the mixed γ-ray–neutron source in the presence of air and treating the solution with dinitrophenylhydrazine gives a precipitate which appears to be the same as that obtained from benzene (*loc. cit.*). By an improved method of elution chromatography, we have now separated this substance into three components. The largest part consists of a dinitrophenylhydrazone, m. p. 300—305°, which appears to be a derivative of an aliphatic dialdehyde and is obtained by irradiation of benzene or of phenol. Paper chromatography with ethanol–butanol–ammonia solution confirmed the identity of the two substances, whilst a solution of phenol, irradiated at an acid pH, yielded a precipitate with dinitrophenylhydrazine, which behaved differently from those obtained from neutral solutions and appears to be a derivative of a quinone.

Experimental.

Materials.—Phenol. This was AnalaR material (Messrs. Hopkin and Williams). Unless otherwise stated, a solution of 2 millimoles of this material in water (100 ml.) was used at a pH ~6 in the irradiations, and one of 0·5 millimole/100 ml. in the experiments with Fenton's reagent.

Water. For the experiments with Fenton's reagent, and for the irradiation with large doses, ordinary distilled water was used. For irradiations with low doses triple-distilled water was used, ordinary distilled water being redistilled in an all-glass still from alkaline permanganate and then from phosphoric acid.

4 : 4′-Dihydroxydiphenyl.—This was prepared by Hirsch's method (*Ber.*, 1899, **22**, 335). Recrystallised from dilute sulphuric acid it had m. p. 273—274° (Schmidt and Schultz, *Annalen*, 1881, **207**, 334, give m. p. 272°).

Catechol. This was purified by conversion into the lead salt, decomposition thereof by hydrogen sulphide, extraction with ether, and one recrystallisation from triple-distilled water.

Quinol. Obtained from Messrs. Hopkin and Williams, this was not further purified.

o-Benzoquinone. This was prepared by Willstätter and Müller's method (*loc. cit.*).

Experiments with Fenton's Reagent.—The ferrous and ferric sulphates used were of AnalaR quality (Messrs. Hopkin and Williams). The hydrogen peroxide was 90% material, free from stabilisers, suitably diluted. Experiments were carried out as described previously (Loebl, Stein, and Weiss, *J.*, 1949, 2074). Separate solutions of hydrogen peroxide and ferrous or ferric sulphate were run simultaneously into a stirred solution of acidified phenol. As complex-forming agents phosphoric acid (AnalaR) and sodium fluoride (puriss.; Messrs. Hopkin and Williams) were used.

Irradiations.—These were carried out as described previously (Farmer, Stein, and Weiss, *J.*, 1949, 3241). A Victor Maximar set was used at 200 kv and 15 mA, without filtration. The dose, determined according to Day and Stein's method (*Nature*, 1949, **164**, 671; *Nucleonics*, 1951, **8**, No. 2, p. 34) was approx. 2300 E.U./min. when 200 ml. of the solution were irradiated, and approx. 3200 E.U./min. when 100 ml. solution were irradiated. At the wave-length of the *X*-rays used, 1 E.U. equals approximately 1 roentgen. Experiments were carried out (*a*) in air, (*b*) in a vacuum (the solution being freed from air by passage through it of purified nitrogen, followed by evacuation), or (*c*) in solutions saturated with oxygen (oxygen being bubbled through the solution for at least 30 minutes before irradiation). The pH values stated in the experiments were maintained by the addition of sulphuric acid (AnalaR) for pH values lower than 3, by phosphate buffers (Na_2HPO_4 and KH_2PO_4, AnalaR) between pH 3 and 8, and by sodium hydroxide (AnalaR) above pH 8. Phosphate ions do not interact with the radicals.

Detection of Resorcinol (cf. Krauskopf and Ritter, *J. Amer. Chem. Soc.*, 1916, **38**, 2182).—To synthetic mixtures containing phenol, catechol, and quinol in amounts similar to those obtained in experiments with Fenton's reagent or with large doses of irradiations, were added 4 mg. of cobalt chloride and various amounts of resorcinol, the resulting mixture being diluted to 100 ml., to which 2 ml. of ammonia solution (*d* 0·88) were added. Transient intense green coloration, changing to brown, was obtained, the lowest resorcinol concentration yielding a definite result being 0·001 millimole/100 ml., in the presence of 0·5 millimole of phenol. In experiments with Fenton's reagent or *X*-rays, even when the amount of catechol + quinol amounted to 0·05 millimole or more, no positive reaction for resorcinol was obtained. If to such solutions 0·001 millimole or more of resorcinol was added the colour reaction was positive.

Determination of Catechol and Quinol.—Method 1. This method was essentially that of Baernstein (*loc. cit.*). In experiments with Fenton's reagent, ether-extraction was continued for 16 hours. In radiation experiments extraction was unnecessary and the determinations were carried out directly on the reaction mixture. In both cases sodium sulphite was added before analysis. Catechol was determined by lead acetate at pH 6·5 in the presence of a pyridine buffer, the precipitate being filtered off in a sintered-glass crucible and then dissolved in acetic acid; the lead was precipitated as iodate, and IO_3^- determined in this precipitate by the liberation of iodine from potassium iodide, and titration against 0·2N-sodium thiosulphate. In the filtrate of the first (catechol) precipitate, the quinol, and subsequently the phenol, was determined by iodination at fixed pH values, potassium iodide and a bromide–bromate solution being used. The liberate diodine was titrated as above, by a potentiometric method, with a platinised platinum electrode and a dip-type calomel electrode, in conjunction with a Cambridge pH meter set for E.M.F. measurements. Readings of the E.M.F. (E) were taken for increments (V) of 0·1 ml. of titrant in the vicinity of the end point, and the end point was determined graphically from a plot of dE/dV against V. Other particulars of the method, preparations of the standard solutions, and general procedure were as in Baernstein's paper (*loc. cit.*). Control analyses on synthetic solutions containing phenol, catechol, and quinol showed that the method was accurate within $\pm 4\%$, when the amounts present were of the order of 0·1 millimole/100 ml., but the procedure is very tedious. 4 : 4′-Dihydroxydiphenyl, when present, interfered, leading to "recoveries" of phenol greater than the amount originally present, but apparently it did not interfere with the determination of quinol or catechol.

Method 2. (i) The reagent solution was prepared immediately before use by adding 2 ml. of 15% titanium(III) chloride or sulphate solution to 5 ml. of 2N-sulphuric acid, and diluting the whole to 200 ml. with water. An aliquot of the neutral, irradiated solution was made up to exactly 50 ml. and transferred to a 100-ml. measuring flask. To this was added 5 ml. of a disodium hydrogen phosphate solution (10 g. of anhydrous salt in 100 ml. of water) and then, with constant stirring, drop by drop, 2 ml. of the freshly made reagent; the pH of the mixture was then 7·9—8·0. After 30 minutes the solution was made up to 100 ml. and the intensity of the yellow colour measured. Phenol, quinol, and 4 : 4′-dihydroxydiphenyl do not interfere. Hydrogen peroxide interferes to some extent and must be absent for accurate determinations. A calibration curve was obtained by using a Spekker colorimeter, Ilford filter 601, and a 3-cm. cell. Full optical density was reached at room temperature only after about 30 minutes, but the process could be accelerated by warming. We did not do so, since the simultaneous determination with Folin's reagent also took about 30 minutes. Optical density was a linear function of the concentration of catechol in the range 1—7 micromoles/100 ml. For the colour formation of catechol with Ti^{3+}, cf. Piccard (*Ber.*, 1909, **42**, 4343).

(ii) The amount of (quinol + catechol) in the solution was determined by Folin's reagent at an acid pH, and not in alkaline solution as usual. An aliquot of the irradiated solution was made up to 25 ml. with water and transferred to a 100-ml. measuring flask. To this was added 5 ml. of a solution of potassium dihydrogen phosphate (10 g. in 100 ml. of water), and then exactly 1 ml. of Folin–Ciocalteau's reagent. This reagent was prepared by treating sodium tungstate (100 g.) and molybdate (25 g.) with water (700 ml.), 85% phosphoric acid (50 ml.), and concentrated hydrochloric acid (100 ml.), boiling the whole gently with reflux for 10 hours, adding lithium sulphate (150 g.), water (50 ml.), and bromine (a few drops), then boiling the mixture without a condenser for 15 minutes in a fume cupboard, cooling it,

diluting it to 1 l., and filtering it through a fritted-glass filter after 3 days (cf. Snell, "Colorimetric Methods of Analysis," 1937, Vol. II, p. 197).

After addition of the reagent, the pH of the test solution was 2·6—2·7. The mixture was then immersed into a boiling-water bath for exactly 30 minutes and diluted immediately afterwards with cold water to 100 ml.; the intensity of the colour was then measured; as comparison solution an unirradiated phenol solution treated in the same manner was used. Under these conditions phenol and 4 : 4′-dihydroxydiphenyl do not interfere. Hydrogen peroxide interferes only to a small extent, when present in comparable quantities.

(iii) The calibration curves for the determination of catechol and of quinol by Folin's reagent (Spekker colorimeter, Ilford filter 608, 3-cm. cell) show that the optical density is a linear function of the concentration of catechol up to about 1 micromole/100 ml., and also a linear function of the concentration of quinol in the range 1—5 micromoles/100 ml. The volume of the irradiated solution used in one test was 2—3 times greater for the determination of catechol by Ti^{3+} than the volume used in the Folin test. Fig. 7 shows the influence of temperature and time of heating on the optical density obtained. The annexed Table shows some results obtained on synthetic mixtures.

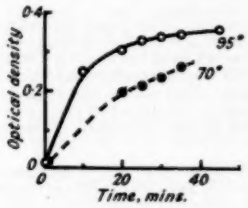


FIG. 7.

Influence of time and temperature of heating on the colour development in the determination of catechol by Folin's reagent.

Analysis of synthetic mixtures of quinol and catechol by method 2 (quantities in micromoles/100 ml.).

Calculated		Found	
Quinol	Catechol	Quinol	Catechol
1·70	0·355	1·45, 1·6, 1·7, 1·5	0·35, 0·34, 0·36, 0·35
0·85	0·355	0·7, 0·8, 0·75	0·36, 0·355, 0·345

Detection of Hydrogen Peroxide.—To ascertain the presence or absence of hydrogen peroxide in the irradiated solutions, tests described by Feigl ("Qualitative Analysis by Spot Tests," 1939) were used. Even in the presence of catechol, that employing an acid solution of a Ti^{3+} salt can be used. We have mainly relied on the sodium carbonate-cerium(III) sulphate test. The reagent is nearly colourless and gives a strong red-to-brown colour with traces of hydrogen peroxide. With the unirradiated phenol solution and with the same solution after irradiation at a neutral pH, this gave a greyish precipitate, but no red colour, whilst if a trace of hydrogen peroxide were added to the solutions, the red colour reaction could be observed, not masked by the reaction with phenol. Whilst no peroxide was thus found to be present in neutral irradiated solutions, a weak positive reaction was obtained with irradiated acid solutions.

Ratio of Quinol : Catechol in Solutions irradiated at an Acid pH.—A 0·2% solution (100 ml.) of phenol was irradiated at pH 2·2, and then treated with dilute aqueous sulphur dioxide drop by drop, till all the colour disappeared, and then 1 drop was added in excess. Any excess of sulphur dioxide interferes in the determination by Folin's reagent, and it was therefore driven from the solution by evacuation and boiling out at room temperature, or alternatively by aeration at 50°. Owing to this procedure, the results were not very accurate for quinol, but quite reliable for catechol. For a dose of 6×10^4 E.U. the amount of catechol found was $(3{\cdot}4 \pm 0{\cdot}2) \times 10^{-6}$ mole, whilst the yield of quinol was $2—3 \times 10^{-6}$ mole, the ratio varying from 5 : 1 to 8 : 1. Comparison of these results with those shown in Fig. 1, obtained in neutral solutions, shows that the yield of catechol has decreased and that of quinol increased. This is in qualitative agreement also with the results obtained by Baernstein's method on solutions irradiated with higher doses, as shown in Table II. Reduction with sulphur dioxide gives the corresponding dihydroxybenzene from quinones. Whilst this is likely to be so in the present case, we have no independent proof, that the quinonoid product, after reduction, appears in the form of catechol or quinol, respectively. However, the results of experiments carried out in a vacuum (below) seem to support this.

Irradiations in a Vacuum.—A few experiments were carried out to determine the yield of hydrogen in irradiations in a vacuum. The apparatus used for evacuation, irradiation, and analysis were as described previously (Farmer, Stein, and Weiss, *loc. cit.*). When 100 ml. of a neutral 0·2% solution of phenol were irradiated with a dose of $3{\cdot}6 \times 10^5$ E.U. the yield of hydrogen (calc. in terms of H atoms, cf. Stein and Weiss, *J.*, 1949, 3245) was $6{\cdot}2 \times 10^{-6}$ equivalent, whilst a similar irradiation carried out at pH 2·2 yielded only $2{\cdot}4 \times 10^{-6}$ equivalent. Both the neutral and the acid solution remained colourless after irradiation, showing that, in the absence of oxygen, quinone formation could not take place. In a vacuum, the aryl radicals may react with a molecule of phenol or another radical (Stein and Weiss, *loc. cit.*).

Experiments in a vacuum (where quinone formation does not occur) yielded values for catechol and quinol in acid solution (Table II) which are in qualitative agreement with those obtained in the presence of oxygen (see previous section). The reduced yields of hydrogen in acid solutions indicate perhaps the presence of aryl radicals, which react with hydrogen atoms more rapidly than do the aryl radicals present in neutral solution, thus reducing the number of hydrogen atoms which can yield hydrogen molecules.

Absorption Spectra and Colorimetric Measurements.—The ultra-violet and visible absorption spectra shown in Figs. 4, 5, and 6, as well as the results shown in Fig. 2, were obtained by using a Unicam S.P. 500 instrument, and appropriate silica or glass cells. Fig. 3 was obtained with a Spekker colorimeter with Ilford filter No. 601, having a maximum transmission at approx. 430 mμ.

Fig. 2 was obtained by taking, at the pH at which the irradiation was carried out, the complete spectra of solutions irradiated at pH 2·2 with the doses stated, and plotting the optical densities obtained at $\lambda_{max.}$, *i.e.*, 290 mμ. Fig. 3 was obtained by irradiating the solutions at the pH values stated with a constant dose of 6×10^4 E.U. and then bringing every solution to a pH value of $5{\cdot}5 \pm 0{\cdot}1$ (controlled with a Cambridge pH meter and a glass electrode) before determination of the optical density. The curves shown in Fig. 4 were obtained by measuring the unirradiated against the irradiated solution in the Unicam instrument.

Colour Reactions with o-*Phenylenediamine.*—To the acid solution containing *o*-benzoquinone (extracted from the original ethereal solution) there was added 1 ml. of a saturated solution of *o*-phenylenediamine in 2N-sulphuric acid. The concentration of the quinone affected the time for formation of the green colour and appearance of the red fluorescence. This process may be accelerated by gentle warming. The formation of the red colour with *p*-benzoquinone is faster. Neutralising the *o*-quinone–diamine solution causes the fluorescence to disappear, the colour to change to yellow, and a precipitate to appear. From concentrated reaction mixtures a precipitate appears even in acid solutions. These products are being investigated.

Enzymic Experiments.—Tyrosinase was prepared from mushrooms by Mr. F. K. Duxbury by Jensen and Tenenbaum's procedure (*J. Biol. Chem.*, 1942, **145**, 293; 1943, **147**, 737). The tyrosinase solution (1 ml.) was added to 0·2% phenol solution (100 ml.) in the presence of a phosphate buffer at pH 7. After 30 minutes at room temperature, the solution was made N. with sulphuric acid, and then the colour test with *o*-phenylenediamine was carried out, the spectrum of the resultant solution being shown in Fig. 5.

Experiments with Mixed Neutron–γ Rays.—These were carried out as described previously (Stein and Weiss, *J.*, 1949, 3254). The mixture was separated by elution chromatography on alumina. The presumed dialdehyde derivative was eluted in the 1 : 1 light petroleum–benzene fraction. Recrystallised from light petroleum, it had m. p. 300—305° (preheating to 290°) (cf. Baker, Ollis, and Zeally, *J.*, 1951, 206). Acid solutions of phenol, when irradiated, did not yield this product in large quantities, but gave instead a product which was extremely strongly adsorbed in alumina. This dinitrophenylhydrazone changes colour on treatment with ammonia, as do derivatives of acids. Dinitrophenylhydrazones, *e.g.*, that of *p*-benzoquinone, behave similarly. On paper chromatography the product obtained from the irradiated acid solution (Whatman filter paper No. 1, butanol–ethanol–ammonia solution) behaved quite differently from the derivatives obtained by irradiation of benzene or phenol in neutral solution, and exhibited R_F values similar to those of quinone derivatives. We hope to investigate these points further.

We thank Professor G. R. Clemo, F.R.S., for his interest, Dr. D. G. I. Felton and Dr. F. J. McQuillin for valuable advice and discussion, Mr. F. K. Duxbury for the tyrosinase preparation, and Mr. P. Sumner for assistance. The irradiations were carried out with the co-operation of the Radiotherapy Department of the Royal Victoria Infirmary, for which we thank Dr. F. T. Farmer and Mr. M. J. Day. This investigation was supported by the North of England Council of the British Empire Cancer Campaign, to which we express our thanks.

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[*Received, May 2nd,* 1951.]

724. *Some Free-radical Reactions of Chlorobenzene. The Action of the Hydrogen Peroxide–Ferrous Salt Reagent and of X-Rays on Aqueous Solutions of Chlorobenzene.*

By G. R. A. Johnson, Gabriel Stein, and Joseph Weiss.

The reactions of chlorobenzene in aqueous solution with OH and HO_2 radicals, produced by means of Fenton's reagent and by *X*-rays, have been studied. The three chlorophenols were formed in both cases. Their relative proportions have been estimated, and the dependence of this ratio on the pH investigated.

The position occupied by the chlorine atom is also attacked, and dechlorination and formation of diphenyl result. The extent of this reaction is apparently not influenced by pH.

The results indicate that the presence of the chlorine substituent in the aromatic ring has an effect similar to that of the nitro- or carboxy-groups (*J.*, 1949, 2074; 1950, 2704; 1951, 405), but different from that of the hydroxyl group (preceding paper).

Possible reaction mechanisms are discussed. Separation of the chlorophenols by paper chromatography is described.

In previous papers it has been shown that the action of ionising radiations, *e.g.*, *X*-rays, on dilute aqueous solutions is due to free radicals (Weiss, *Nature*, 1944, **153**, 748; *Brit. J. Radiol.*, Suppl. I, 1947, etc.). When solutions containing oxygen are irradiated with small doses of radiations, in the presence of suitable acceptors, the reactions are somewhat similar to those obtained by the hydrogen peroxide–ferrous salt reagent (Fenton's), and are due to OH and HO_2 radicals.

The present paper records results for the corresponding reactions with chlorobenzene. In particular, two points seemed of interest. First, whether the directive influence of the chlorine atom would be similar to that of the *meta*-directing nitro- and carboxy-groups (Loebl, Stein, and Weiss, *J.*, 1949, 2074; 1950, 2704; 1951, 405), or the *ortho–para*-directing hydroxyl group (preceding paper). Secondly, whether any dechlorination which occurs is due to the OH and HO_2 radicals, as in the case of nitrobenzene, rather than to the hydrogen atoms, and its dependence on pH.

That dechlorination by *X*-rays takes place in solution has been shown by Minder (cf. Minder and Liechti, *Radiol. Clin.*, 1949, **18**, 108). In the electrolytic oxidation of chlorobenzene in aqueous media (Fichter and Adler, *Helv. Chim. Acta*, 1926, **9**, 279; Fichter, "Organsiche Elektrochemie," 1942, p. 102), the formation of *p*-benzoquinone was observed, and chloride ions were found in the solution. Fichter interprets his results by assuming *p*-chlorophenol to be the main primary product of the reaction.

After reaction of Fenton's reagent with chlorobenzene, Merz and Waters (*J.*, 1949, 2427) isolated *o*-chlorophenol.

In agreement with the principles discussed in the preceding paper, we have employed a saturated aqueous solution of chlorobenzene, and sufficiently small doses of radiation to ensure that the whole of the radiation reaction occurred in the presence of dissolved oxygen in the solution. The solubility of chlorobenzene in water is only 0·05 g./100 ml. at 30° (cf. "Handbook of Chemistry and Physics," Chem. Rubber Publ. Co., 1949, p. 677). However, we have shown previously in the case of benzene (Stein and Weiss, *J.*, 1949, 3245) where the solubility in water is only 0·09 g./100 ml. (at 22°) that as little as 0·02 g. of benzene per 100 ml. will give a yield which is only 10% lower than the maximum yield. In the present case we have also found that the reaction proceeds readily, and gives yields comparable to those obtained in the case of benzene and nitrobenzene. Thus, the concentrations of these substances in aqueous solutions are sufficient to ensure a reaction velocity which prevents the recombination of the primary radicals (cf. Weiss, *loc. cit.*).

The Action of X-Rays. Determination of the Isomeric Chlorophenols.—In the present case we combined the results from infra-red spectrum analysis and from paper chromatography, for the determination of the chlorophenols. Thus, from the infra-red spectra the presence and the quantity of the *o*- and especially the *p*-derivative could be established with some certainty; on the other hand, paper chromatography yielded reliable results for the *o*- and,

particularly, the *m*-derivative. Combination of these procedures established beyond doubt that all three isomers are formed, their relative proportions depending on the pH. From the quantitative point of view the results obtained from the infra-red spectroscopy (Table) were more accurate. In addition to these products, the presence of phenol was also shown by the infra-red analysis.

The results obtained from the paper chromatography confirmed the presence of the three isomers, and of phenol, and have shown that apparently chlorodihydroxybenzenes are not present in comparable amounts.

The relative ratios of the three isomeric chlorophenols are similar to those obtained in the cases of nitrobenzene and of benzoic acid (Loebl, Stein, and Weiss, *loc. cit.*) but differ from those obtained with phenol, where no *m*-derivative was found (see Table).

Action of X-rays on aqueous solutions of chlorobenzene (200 ml. of solution irradiated with a dose of $3{\cdot}25 \times 10^4$ E.U.).

pH:	2	6	12
Total solid residue (including phenol and diphenyl) (mg.) ...	2·4	2·0	2·3
Relative ratios (%):			
ortho	25—30	15—20	35—40
meta	30—35	20—25	20—25
para	35—40	50—60	35—40

The Action of Fenton's Reagent.—The hydrogen peroxide–ferrous salt reagent was used in acid solution, at pH ~1. Under these conditions, the procedure described for nitrobenzene being used, only a slow and mild attack takes place, resulting in the formation of small amounts of chlorophenols, the solution at the end of the reaction being pale yellow. Infra-red analysis showed *ortho* 40—45, *meta* 20—25, and *para*-isomer 20—25%. The relatively large proportion of the *o*-derivative was confirmed in several experiments. Paper chromatography yielded results similar to those obtained in the case of *X*-rays, and secondary products were again absent.

In view of the relative inaccuracy of these determinations, it is impossible to draw conclusions beyond the fact that all three isomeric chlorophenols are formed, their ratios not differing materially from those obtained by the use of *X*-rays, and in qualitative agreement with those obtained in the case of nitrobenzene and benzoic acid.

The Dechlorination of Chlorobenzene.—The formation of the chlorophenol is the result of a sequence of reactions:

$$H_2O \rightsquigarrow H + OH \quad . . . . . \quad (1)$$
$$H + O_2 \longrightarrow HO_2 \quad . . . . . \quad (1a)$$
$$C_6H_5Cl + OH \longrightarrow C_6H_4Cl + H_2O \quad . . . . . \quad (2)$$
$$C_6H_4Cl + OH \longrightarrow C_6H_4Cl{\cdot}OH \quad . . . . . \quad (3)$$

or of the equivalent reactions of the aryl radical with HO_2. Furthermore, the chlorine atom could behave in the same way as a hydrogen atom, and thus be removed:

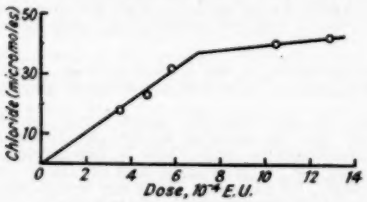
$$C_6H_4Cl + OH \longrightarrow C_6H_3 + HOCl \quad . . . . . \quad (4)$$

A similar reaction (denitration) has been observed in the case of nitrobenzene (Loebl, Stein, and Weiss, *loc. cit.*). In the present case dechlorination occurs and chloride ions are present in the solution after the irradiation. Irradiation of 200 ml. of a solution with a dose of $5{\cdot}85 \times 10^4$ E.U. produced $3{\cdot}2 \times 10^{-5}$ mole of chloride ion at pH 2 or 6 and $3{\cdot}3 \times 10^{-5}$ mole at pH 12 (determined turbidimetrically). The dechlorination reaction is thus apparently not influenced by the pH. Moreover, the figure shows that it is more rapid in the presence of oxygen, indicating that the removal of chlorine proceeds more readily by means of OH or HO_2 than of hydrogen atoms. The analytical accuracy in the present case is very good and lends further support to the less accurately established but similar conclusions for nitrobenzene. The favourable effect of oxygen is remarkable, since reductive dechlorination of chlorobenzene is known to proceed fairly readily (Kelber, *Ber.*, 1917, **50**, 309; Busch and Schmidt, *Ber.*, 1929, **62**, 2617). Our findings are supported, however, by those of Fichter (*loc. cit.*) that an extremely ready dechlorination of chlorobenzene occurs in anodic oxidation processes.

With a dose of $3{\cdot}25 \times 10^4$ E.U. approximately 18 micromoles of chloride ion were produced (see figure) under conditions in which the total production of chlorophenols was of the order of 5 micromoles (Table I). We have no reliable quantitative data regarding products of the dimerisation of the aryl radical, but one may conclude that on the whole the dechlorination reaction seems to be favoured. This view is supported by the fact that apparently very little

dichlorodiphenyl is formed in the reaction, whilst diphenyl was found in relatively large quantities. The results, therefore, seem to establish definitely the following salient points: the removal of the existing substituent occurs in a process which is apparently independent of the pH, whilst the introduction of the hydroxyl group occurs in a reaction which is influenced by the pH. In the case of benzene, quantitative evidence has been produced (Stein and Weiss, *J.*, 1949, 3256) in favour of a reaction mechanism involving two distinct steps, namely, those equivalent to reactions (2) and (3), and *not* a reaction mechanism involving a direct displacement, in which the total process coalesces into a single step. The evidence obtained in the present paper supports this view. Moreover the results indicate strongly that in the present reaction the chlorine atom has a directive influence similar to that of the nitro- or carboxy-group. The influence of chlorine in aromatic substitution (cf. Ingold and Shaw, *J.*, 1949, 575; Bird and Ingold, *J.*, 1938, 918) is composed of a " $-I$ " and a " $+T$ " effect. Our results seem to indicate the preponderence of the " $-I$ " effect in the particular step in which the OH radical enters into the molecule. Regarding the predominantly *para*-type of substitution, our results are in agreement with the results and views of Hey (*J.*, 1934, 1957; Augood, Hey, Nechvatel, and Williams, *Nature*, 1951, **167**, 725) on homolytic aromatic substitution by free radicals in solution.

These results also seem to support De la Mare's views (*J.*, 1949, 2871) on the importance of electromeric polarisability in some reactions which may perhaps have some bearing on the present case. In particular, it is possible that the increased formation of the *ortho*-derivative



Formation of chloride by the action of X*-rays on chlorobenzene in aqueous solutions, in the presence of air (showing the diminished rate of formation on exhaustion of the oxygen in the solution).*

in the case of Fenton's reagent is due to the ionic nature of one of the reactive entities. In the preceding paper we have already described some possible effects of the $Fe(OH)^{2+}$ complex.

Our results seem to be in general agreement with the results of other workers regarding free-radical reactions of similar type in solutions. It is inadmissible to conclude, however, without establishing first a complete identity of the reaction mechanisms and of the type of reactants, that other free-radical reactions must yield very similar results or that reactions giving somewhat similar results are necessarily free-radical reactions.

Experimental.

Materials.—The water used in the present experiments was of the quality described in the preceding paper. The chlorobenzene (B.D.H.) was shaken with aqueous potassium hydroxide, washed with water, dried, and distilled at atmospheric pressure. The *o*-chlorophenol (B.D.H.) was freed from phenol by shaking it with 10% aqueous potassium carbonate, the alkaline solution being extracted with ether and then acidified, and the separated *o*-chlorophenol dried ($CaCl_2$) and distilled at atmospheric pressure. *m*-Chlorophenol was prepared according to Holleman and Rinkes's procedure (*Rec. Trav. chim.*, 1911, **30**, 81) and recrystallised from light petroleum; it had m. p. 26—28°. The *p*-chlorophenol (B.D.H.) was not further purified.

Experiments with Fenton's Reagent.—Ferrous sulphate (AnalaR, Messrs. Hopkins and Williams) and hydrogen peroxide (Laporte, 90%, stabiliser-free) were used, the experimental procedure being as for nitrobenzene (*loc. cit.*). Separate solutions of the ferrous salt and the dilute hydrogen peroxide were run simultaneously into the acidified (pH approx. 1) saturated, aqueous solution of chlorobenzene. The acid solution was extracted with ether, the organic layer treated with 10% sodium hydroxide solution, and this extract washed with ether, acidified, and extracted with ether. The last ethereal extract was evaporated and the residue submitted either to infra-red analysis or to paper chromatography. From the neutral fraction of the products, which remained in the ethereal extract of the acid reaction mixture, after treatment with alkali, there was obtained by elution chromatography diphenyl (m. p. 67°, not depressed on admixture with authentic specimen) and a second small fraction of a crystalline material (possibly some dichlorodiphenyls).

Irradiations.—These were carried out as described previously (cf. preceding paper, and Farmer, Stein, and Weiss, *J.*, 1949, 3241), the dose being measured by Day and Stein's method (*Nature*, 1949, **164**, 671; *Nucleonics*, 1951, **8**, No. 2, 34), in terms of the Gray–Read Energy Unit (E.U.), which is approximately equal to the roentgen. Their radiated solutions were treated similarly to those

resulting from experiments with Fenton's reagent. In these cases the quantities of diphenyl and of dichlorodiphenyl were too small for definite identification. The products of six irradiations were combined for analysis by either method.

Infra-red Analysis.—These were carried out with a Hilger D.209 single-beam instrument with nitromethane as solvent. With this method, reliable and reproducible results could be obtained for *p*-chlorophenol, and, in the case of experiments with Fenton's reagent where larger yields were obtained, also for *o*-chlorophenol. The results for the *m*-derivative were, however, not very accurate. The presence of phenol was clearly indicated in all the spectra.

Paper Chromatography.—It was not possible to separate the isomeric chlorophenols themselves by paper chromatography. Coupling with diazotised *p*-nitroaniline, which strongly coloured derivatives, and subsequent paper chromatography, was no better. Since it was possible to separate the isomeric hydroxybenzoic acids by paper chromatography (*loc. cit.*), we attempted coupling with derivatives which would introduce an acid group into the molecule; *p*-aminobenzoic acid was tried unsuccessfully. Finally, coupling with sulphanilic acid gave a separation of the isomers which could be used for the qualitative identification of, especially, the *m*-derivative. Thus, the mixture of the three isomeric chlorophenols (containing also some phenol) was coupled with diazotised sulphanilic acid at 0° according to Snell's procedure ("Colorimetric Methods of Analysis," 1937, Vol. 2). The solution of the diazoates was kept at 0°, acidified, and extracted with *iso*butyl alcohol, the resulting extract was run on Whatman paper No. 1, in a mixture of *iso*butyl alcohol 70, ammonia solution (*d* 0·88) 25, water 80, and ethanol 25 parts by vol., the non-aqueous layer being used. Chromatograms were run upward in a constant-temperature room. The *m*- is separated well from the *o*- and the *p*-isomer and also from the phenol, but the *o*- and *p*-derivatives are not separated well from each other. From the *o*-chlorophenol two spots were obtained in the chromatogram due, perhaps, to coupling in two alternative positions. One of these spots coincides with that obtained from the *p*-derivative. The other is unique, and can be used for the identification of the *o*-derivative. The *p*-derivative does not, in the presence of *o*-isomer, produce a unique spot, and cannot be identified with certainty from the chromatogram alone. This method thus confirmed the presence of the *o*- and the *m*-derivative, which have been established also be infra-red analysis.

Determination of Chloride.—This was carried out according to the method of Luce, Denis, and Akerlund (*Ind. Eng. Chem. Anal.*, **1943**, **15**, 365) with a Spekker Colorimeter and a neutral grey filter.

The infra-red determinations were carried out in the Infra-red Spectroscopy Section of Imperial Chemical Industries Limited, Billingham; we are grateful to Dr. R. Holroyd and Dr. B. W. Bradford for permission to carry out the measurements, and to Mrs. M. Broomfield for the analyses. We thank Dr. Hanna Loebl for assistance, Dr. F. T. Farmer and Mr. M. J. Day of the Radiotherapy Department, Royal Victoria Infirmary, for help with the *X*-ray irradiations, and the North of England Council of the British Empire Cancer Campaign for financial assistance.

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[*Received, May 2nd,* 1951.]

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725. *A Comparative Study of Persulphates and Benzoyl Peroxide as Initiators of Polymerization in Solution.*

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Polymerizations of styrene, methyl methacrylate, and methyl acrylate initiated by persulphates and benzoyl peroxide, as homogeneous solutions in glycols, have been compared. Persulphates are far more efficient catalyts than benzoyl peroxide, producing faster polymerization and also a polymer of higher molecular weight. Strong sensitivity to oxygen is also observed with persulphates. Polymerization by persulphates in homogeneous solutions therefore has many characteristics in common with emulsion polymerization. Two possible mechanisms are suggested for such difference in behaviour, and one of these is discussed quantitatively.

INORGANIC per-salts such as potassium persulphate have rarely been studied as catalysts of polymerization in solution, their use having been restricted almost entirely to emulsions. This is mainly attributable to the difficulty in dissolving persulphates in the monomers or in the organic solvents in which polymerization is generally carried out. However, the study of the kinetics of vinyl polymerization in homogeneous solution initiated by such catalysts is of interest, not only for its own sake but also because it may throw light on the well-known but unexplained peculiarities of emulsion polymerization (cf. Price, "Mechanism of the Reaction

of the Carbon–Carbon Double Bond," Interscience, 1946, Chap. VI; Harkins, *J. Amer. Chem. Soc.*, 1947, **69**, 1482). Further, a comparative study of the persulphates and benzoyl peroxide as catalysts is also of interest in order to assess how far the persulphates conform to the accepted theories of free-radical polymerization (Bawn, "The Chemistry of High Polymers," Butterworths, London, 1948; Gee and Melville, *Trans. Faraday Soc.*, 1944, **40**, 240).

With this end in view we have studied the polymerization of three monomers, styrene, methyl methacrylate, and methyl acrylate, initiated by potassium, sodium, or ammonium persulphate, and have compared the results with peroxide-catalysed polymerization under identical conditions. The solvents chosen were ethylene, propylene, and diethylene glycols, as we found that these dissolved sufficient both of the monomers and of the persulphates to give a conveniently measurable speed of reaction.

Experimental.

Materials.—Monomers. Styrene was prepared by heating cinnamic acid in presence of quinoline (equal weight) and anhydrous copper sulphate (5% by weight), and a small quantity of quinol was added as inhibitor. Methyl methacrylate was prepared by pyrolytic decomposition of the polymer, and methyl acrylate was purified from the commercial product. Just before use, the monomers were fractionated repeatedly in an all-glass apparatus after the inhibitor had been removed by washing with alkali, and were redistilled.

Glycols. Commercial glycols were purified by two fractional distillations in a vacuum.

Catalysts. Benzoyl peroxide was prepared by Gambarjan's method (*Ber.*, 1909, **42**, 4008). AnalaR grades of persulphates were used as such after being dried in a vacuum-desiccator. Persulphates being very sparingly soluble in glycols, solutions were prepared by shaking, followed by filtration, and were standardized iodometrically just before use.

Polymerization Experiments.—Polymerization was done in Pyrex tubes sealed under vacuum while the contents were frozen in liquid air. The thermostat was kept constant to $\pm 0{\cdot}1°$. The solvent : monomer ratio in all the solvents was 5 : 1. In polymerization of styrene, especially at high temperatures, there was some tendency for the polymer to be formed as a coarse colloidal suspension which could be separated only with difficulty by the usual method of precipitation with methyl alcohol. However, addition of ethyl alcohol saturated with sodium acetate brought about rapid coagulation of the polymer. This was washed with water and alcohol, redissolved in benzene, precipitated again with methyl alcohol, dried *in vacuo* at 45°, and weighed.

With methyl methacrylate, manipulation was simplified by the fact that the polymers coagulated readily on addition of methyl alcohol. From methyl acrylate the polymer separated as usual as a pasty mass, which caused some difficulty in obtaining it free from monomer.

During these experiments it was noticed that, when persulphates were used as catalysts, the polymers were formed homogeneously throughout the ampoule, but with benzoyl peroxide, they tend to form lumps. This is comparable with Heuser and Perry's observation (*J. Phys. Coll. Chem.*, 1949, **53**, 1175) that the lumps are produced when oil-soluble catalysts are used in emulsion polymerization. Owing to the strong inhibition caused by the residual oxygen in the system, some of the experiments were performed in as complete absence of oxygen as practicable. This was achieved by cooling the ampoules in liquid air, evacuating the tubes, flushing them with nitrogen (washed free from oxygen by passage through towers filled with alkaline pyrogallol solution), and then warming them to room temperature, cooling again, evacuating and then flushing again with nitrogen, the procedure being repeated three times before sealing.

As the reaction we have studied is quite fast, and as some time is required for the monomer to dissolve completely when placed in the thermostat, the yields for low conversions are subject to greater error, as shown by the lower reproducibility of the results in this range.

Viscosity Measurements.—The viscosity was measured of solutions of less than 1% concentration in an Ostwald viscometer with an influx time of about 200 seconds with acetone. The temperature of the thermostat was checked to $\pm 0{\cdot}02°$. The intrinsic viscosity, $[\eta]$, was obtained by graphical extrapolation to zero dilution of $\eta_{sp.}$/concentration plotted against concentration.

Results.—Styrene. Some typical results of experiments with styrene are summarized in Figs. 1—3. Full lines in all the figures represent results with persulphates, and the broken lines those with benzoyl peroxide. In Figs. 1 and 2 are shown the yield curves for experiments at 80° and 70° with diethylene glycol as solvent, and Fig. 3 represents experiments carried out at 61° (solvent, propylene glycol), all the residual air having been replaced by nitrogen before the ampoules were sealed. Our results show the following features.

(1) The persulphates are far stronger initiators than benzoyl peroxide; *e.g.*, our experiments at 80° (Fig. 1) show that potassium persulphate is about 50 times more efficient than benzoyl peroxide. This is evident on comparing curves 2 and *A* which show nearly equal speed, but the former contains $2{\cdot}2 \times 10^{-3}$M-persulphate whereas the latter contains 110×10^{-3}M-peroxide. However, at lower temperatures, this marked disparity tends to diminish; *e.g.*, at 61° (Fig. 3; cf. curves 1 and *D*) the ratio of efficiencies is only about 30.

(2) The intrinsic viscosity of the polymers formed by the persulphate initiation is greater than that of those obtained by use of benzoyl peroxide; *e.g.*, at 80° seven samples of polymers chosen at

random prepared from persulphate catalysis gave [η] values of 0·82, 0·56, 0·55, 1·17, 0·885, 0·99, 1·17, average = 0·88; and the corresponding [η] values for benzoyl peroxide polymer are 0·21, 0·20, 0·21, 0·29, 0·40, average = 0·26. Similarly, at 61°, the corresponding ranges of [η] are *ca.* 1·25 and 0·35—0·65, respectively. Hence, the viscosities of the persulphate-initiated polymers are roughly 3 times those of the peroxide-initiated polymers. When calculated in molecular weights according to the Staudinger–Mark equation (Goldberg, Hohenstein, and Mark, *J. Polymer. Sci.*, 1947, **2**, 503), *viz.*, [η] =

FIG. 1.

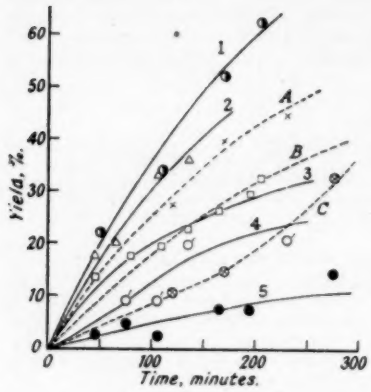
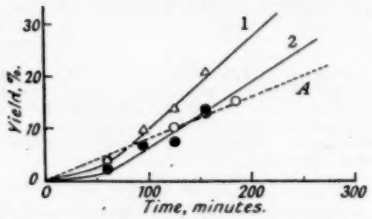


FIG. 2.

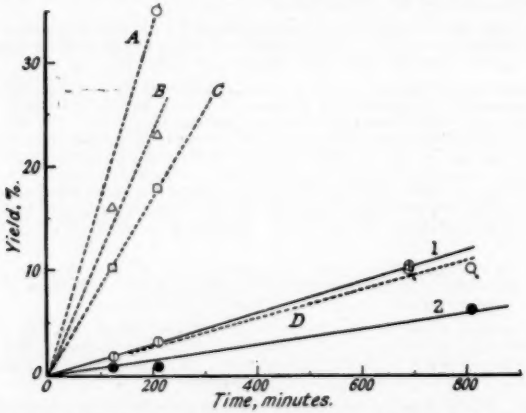
Polymerization of styrene in diethylene glycol at 70°.



(*A*): *Catalyst*, Bz_2O_2—110 × 10^{-4} *mol./100 c.c. of monomer.*
(1), (2): *Catalyst*, $K_2S_2O_8$—2·5 × 10^{-4} *and* 2·2 × 10^{-4} *mol./100 c.c. of monomer, respectively.*

FIG. 3.

Polymerization of styrene in propylene glycol at 61° (nitrogen atmosphere, under reduced pressure).



(*A*), (*B*), (*C*), (*D*): *Catalyst*, Bz_2O_2—60 × 10^{-4}, 30 × 10^{-4}, 15 × 10^{-4}, *and* 3·8 × 10^{-4} *mol./100 c.c. of monomer, respectively.*
(1), (2): *Catalyst*, $K_2S_2O_8$—0·12 × 10^{-4} *and* 0·06 × 10^{-4} *mol./100 c.c. of monomer, respectively.*

KM^a, where $a = 0·62$ and $K = 3·7 \times 10^{-4}$ for toluene, this means that the molecular weight of the former is $3^{1·6}$, *i.e.*, 5·8 times that of the latter. In fact, the viscosity-average molecular weight for one of the samples shown in Curve 2 in Fig. 1 is 64,000, which is unusually high for such dilute solutions of the monomer (1 : 5 by vol.) and with such a high rate of polymerization.

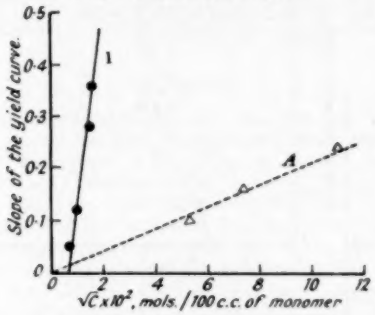
(3) At lower temperatures the differences in viscosity and speed are less marked, as shown by comparing the efficiency ratio and also [η] values for 80° and 61° as in section (2). It should be noted, however, that, although the intrinsic viscosity and hence the molecular weight of the polymer produced by persulphate is much higher than that produced by benzoyl peroxide, the variation in molecular

weight with different concentrations of the same catalyst is quite consistent, the slower the reaction the higher being the molecular weight.

(4) In Fig. 4 are plotted the square roots of the catalyst concentrations against the slopes of the yield curves obtained from Fig. 1. Both plots are straight lines, but that for the persulphate does not pass through the origin. This might be due to the slight inhibition caused by oxygen still present in the evacuated system, for Baxendale, Evans, and Kilham (*Trans. Faraday Soc.*, 1946, **42**, 668) found a

FIG. 4.

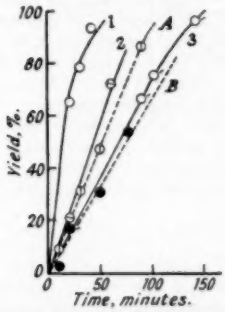
Plot of the rate of polymerization at 80° against the square root of catalyst concentration for polymerization of styrene in diethylene glycol.



(1) $K_2S_2O_8$. (*A*) Bz_2O_2.

FIG. 5.

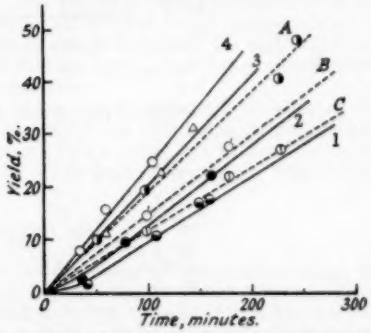
Polymerization of methyl methacrylate in diethylene glycol at 80°.



(1), (2), (3) : *Catalyst,* $K_2S_2O_8$—$3·7 \times 10^{-4}$, $2·8 \times 10^{-4}$, and $1·9 \times 10^{-4}$ *mol./100 c.c. of monomer, respectively.*
(*A*), (*B*) : *Catalyst,* Bz_2O_2—35×10^{-4} *and* 17×10^{-4} *mol./100 c.c. of monomer, respectively.*

FIG. 6.

Polymerization of methyl methacrylate in ethylene glycol at 61° in an atmosphere of nitrogen under reduced pressure.



(*A*), (*B*), (*C*) : *Catalyst,* Bz_2O_2—$1·1 \times 10^{-4}$, $0·84 \times 10^{-4}$, *and* $0·56 \times 10^{-4}$ *mol./100 c.c. of monomer, respectively.*
(1), (2), (3), (4) : *Catalyst,* $K_2S_2O_8$—$2·6 \times 10^{-4}$, $5·3 \times 10^{-4}$, $7·9 \times 10^{-4}$, *and* $10·6 \times 10^{-4}$ *mol./100 c.c. of monomer, respectively.*

similar effect in the curve intended to describe the progress of polymerization of an oxidation–reduction-activated catalyst and attributed it to residual inhibition.

(5) We have found that the persulphate-initiated polymerization of styrene is fairly sensitive to oxygen. It is very difficult to obtain a yield curve which does not show an initial inhibition period, particularly at lower temperatures where the speed of polymerization is lower. With benzoyl peroxide catalysis the effect of oxygen is not marked, as seen from Fig. 2.

Methyl methacrylate. Some typical results with this monomer are presented in Figs. 5 and 6, Fig. 5 illustrating the results of the experiment in diethylene glycol at 80°. In order to show definitely that the inhibition periods in polymerization curves obtained during many preliminary experiments are due

to atmospheric oxygen, we performed a set of polymerization experiments (summarized in Fig. 6) in which the residual air was carefully displaced by nitrogen before sealing; this procedure practically eliminated the inhibition periods of persulphate-catalysed polymerization, though a slight inhibition was still noticeable at very small persulphate concentrations (curves 1 and 2).

The superiority of the persulphates over the benzoyl peroxide is not so striking with this monomer as with styrene. The relative efficiency is of the order of 15, as can be seen by comparing any pair of curves having nearly equal speed, say curves *B* and 3 of Fig. 5. The molecular weight of the persulphate-

FIG. 7.

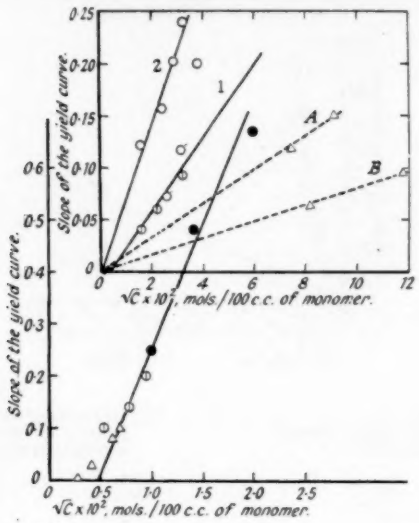
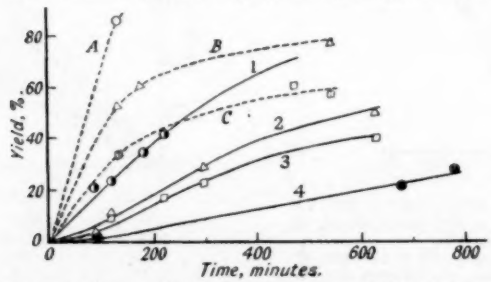


FIG. 8.

Polymerization of methyl acrylate in diethylene glycol at 66°.



(*A*), (*B*), (*C*): Bz_2O_2—39 × 10^{-4}, 27 × 10^{-4}, *and* 15·4 × 10^{-4} *mol./100 c.c. of monomer, respectively.*
(1), (2), (3), (4): $K_2S_2O_8$—0·8 × 10^{-4}, 0·6 × 10^{-4}, 0·3 × 10^{-4}, *and* 0·15 × 10^{-4} *mol./100 c.c. of monomer, respectively.*

catalysed products is also greater, for the [η] values of these polymers are 2·75, 3·1, 2·52, 1·85, 2·0, 2·22, 2·12, 2·24, 1·80, average = 2·28, whereas those for the peroxide-initiated polymers are 1·40, 1·20, 1·20, 1·24, 1·38, average = 1·28. The intrinsic viscosities of the former are therefore about twice those of the latter, indicating that the molecular weight is only $2^{1\cdot3}$, *i.e.* 2·46, times as great, as calculated as before but with $\alpha = 0{\cdot}76$ (cf. Goldberg, Hohenstein, and Mark, *loc. cit.*).

The plot of the square root of the concentration of the catalysts against the slope of the yield curve (Fig. 7, inset; curves 1, 2, *A*, or *B*), like those of other free-radical-activated polymerizations, is a straight line.

Methyl acrylate. Fig. 8 gives some typical yield curves for methyl acrylate polymerized under conditions similar to those with styrene and methyl methacrylate, and the general results are the same, *viz.*, high speed and high oxygen sensitivity of persulphate-catalysed polymerization.

Viscosities of two samples of polymer were measured; one was prepared by using 1×10^{-4} mole of ammonium persulphate per 100 c.c. of monomer and isolated after 25·5% conversion, and the other with $1{\cdot}5 \times 10^{-4}$ mole of benzoyl peroxide after 33·8% conversion, both polymerizations being carried out at 66° and with diethylene glycol as solvent. The former had an intrinsic viscosity of 0·5 in benzene but the latter had only 0·2.

An attempt was made to compare the relative efficiencies of the various persulphates among themselves. We have plotted in Curve 3 of Fig. 7 the rate versus the square root of catalyst concentration for the three persulphates studied. The results fall on a single curve, indicating that the activities of the three persulphates are closely similar if concentrations are expressed in molarities. This is not unexpected, for Green and Masson (*J.*, 1910, **97**, 2283) found that the various persulphates decomposed at essentially the same rate.

Discussion.

The mechanisms of the various thermal, photochemical, and organic peroxide-catalysed polymerizations of vinyl compounds have been studied extensively, and the processes are believed to be initiated by free radicals [cf. *e.g.*, Jones and Melville, *Proc. Roy. Soc.*, 1946, *A*, **187**, 19; Bawn and Whitby, Faraday Soc. Discussion on Labile Molecules (Sept. 1947); Melville, *Proc. Roy. Soc.*, 1937, *A*, **163**, 511; 1938, **167**, 99; Baxendale, Evans, and Kilham, *Trans. Faraday Soc.*, 1946, **42**, 668]. Polymerizations of vinyl compounds initiated by stannic chloride (Williams, *J.*, 1940, 775; Pepper, *Nature*, 1946, **158**, 781), boron trifluoride, aluminium chloride, titanium tetrachloride, and silver perchloride (Evans and Polanyi, *J.*, 1947, 252; Eley and Richards, *Trans. Faraday Soc.*, 1949, **45**, 425; etc.) have also been shown to be chain processes which proceed *via* an ionic mechanism (see Price, *Ann. N.Y. Acad. Sci.*, 1943, **44**, 351).

In view of the structure of persulphates and of instability of the peroxide linkage, we conclude that persulphates also initiate polymerization *via* a free-radical process. This view has been taken by all workers on the persulphate-initiated emulsion polymerization and is supported by the high molecular weight of the polymers formed, the high sensitivity towards inhibitors, and the linear nature of the curve relating the speed of polymerization to the square root of catalyst concentration. Our comparison of the peroxide- and persulphate-initiated polymerization in homogeneous systems shows that the latter have many characteristics in common with the emulsion polymerization, so that any attempt to explain the high speed and high molecular weight of the emulsion process must take account of the ability of potassium persulphate to increase the chain length as demonstrated above.

A few alternative mechanisms can be suggested to account for this high efficiency of the persulphates. The simplest would be to attribute it to a higher rate of initiation of free radicals, but this is ruled out by the fact that, other things being equal, a higher rate of initiation would produce a lowering of the average molecular weight, which is contrary to our observation. This directly follows from the equation,

$$\gamma = -(\mathrm{d}[\mathrm{M}]/\mathrm{d}t)/V_{\mathrm{init.}} = k_p[\mathrm{M}]/\sqrt{k_t V_{\mathrm{init.}}}$$

where γ is the degree of polymerization, $\mathrm{d}[\mathrm{M}]/\mathrm{d}t$ the rate of monomer consumption, $V_{\mathrm{init.}}$ the initiation rate, and k_p and k_t are constants for the propagation and termination rates. There is no *a priori* reason to suppose that the rate of propagation has anything to do with the catalyst, and hence we conclude that this difference is to be accounted for by a low speed of termination of the growing chain by the activated free radical produced by the catalyst.

Of the usual processes of termination of free radicals, *viz.*,

(1) $\mathrm{M}_s^{\bullet} + \mathrm{M}_t^{\bullet} \longrightarrow \mathrm{M}_{s+t}$; (2) $\mathrm{M}_s^{\bullet} + \mathrm{Cat.}^{\bullet} \longrightarrow \mathrm{M}_s\mathrm{Cat.}$; and (3) $\mathrm{Cat.}^{\bullet} + \mathrm{Cat.}^{\bullet} \longrightarrow \mathrm{Cat.}_2$

where Cat.$^{\bullet}$ is the free radical produced by catalyst decomposition, we have to assume that reaction (2) probably predominates over reaction (1) in the case of benzoyl peroxide-catalysed polymerization, leading to a high wastage of the peroxide, whereas in the case of the persulphates this reaction is practically non-existent. This might be due to the low stationary concentration of the free radical produced by the persulphate, or to the inherent inertness of the persulphate radical towards such terminations.

An extreme case of vinyl polymerization where chain termination occurs solely by collision with catalyst fragment has been studied theoretically by the authors (*J. Indian Chem. Soc.*, 1949, **20**, 397). However, in actual practice we can hardly expect such an idealized condition

ever to be fulfilled. Consequently, we now give an analysis of a more complete case which is of particular interest for our present investigation, *viz.*, where the two types of termination, *i.e.*, combination by the two growing radicals (t_1) and termination by catalyst fragemnt (t_2), occur simultaneously. The kinetic framework considered is :

$$\begin{aligned}
&\text{Initiation :} && C \longrightarrow R^{\bullet} \quad \ldots \; k_i \\
&\text{Propagation :} && R^{\bullet} + M \longrightarrow RM_1^{\bullet} \quad \ldots \; k \\
& && RM_1^{\bullet} + M \longrightarrow RM_2^{\bullet} \\
& && RM_m^{\bullet} + M \longrightarrow RM_{m+1}^{\bullet} \quad \ldots \; k_p \\
&\text{Termination :} && RM_m^{\bullet} + RM_n^{\bullet} \longrightarrow RM_{n+m}R \quad \ldots \; k_{t_1} \\
& && RM_n^{\bullet} + R^{\bullet} \longrightarrow RM_nR \quad \ldots \; k_{t_2}
\end{aligned}$$

From the steady-state conditions $d[R^{\bullet}]/dt = 0$ and $d[M^{\bullet}]/dt = 0$, we obtain, on neglecting cubic terms in $[M^{\bullet}]^3$,

$$[M^{\bullet}] = \tfrac{1}{2}\sqrt{\frac{k_i[C]}{k_{t_1}}}\left\{\sqrt{\alpha^2 + 4} - \alpha\right\}$$

where

$$\alpha^2 = \frac{k_i[C]}{k_{t_1}} \frac{k_{t_2}^2}{k^2[M]^2}$$

Consequently,

$$\begin{aligned}
d[M]/dt &= k_p[M][M^{\bullet}] + k_i[R^{\bullet}][M] \\
&= k_p\sqrt{\frac{k_i[C]}{k_{t_1}}}\,[M]\tfrac{1}{2}[\sqrt{\alpha^2 + 4} - \alpha] + k_i[C]
\end{aligned}$$

It will be seen that the maximum value of the term $[\sqrt{\alpha^2 + 4} - \alpha]$ is 2, and this occurs when $\alpha = 0$, *i.e.*, $k_{t_2} = 0$, and the rate expression then reduces to the ordinary form for t_1 termination alone. Under all other conditions $d[M]/dt$ is lower than this normal value, showing that t_2 termination has the effect of reducing the polymerization rate. It will also be noted that the term $[\sqrt{\alpha^2 + 4} - \alpha]$ decreases while [C] increases, showing that the polymerization rate should increase at a rate less than $\sqrt{[C]}$ and this should be more prominent the higher the value of [C]. The general observation of a square-root relation is due to the fact that under the conditions of most experiments α^2 is quite small, which makes the contribution of the term in brackets very small in comparison with that of the term outside the brackets, *i.e.*, $\sqrt{[C]}$. We can get an idea of the approximate value of α from the rate constants involved in it. Some of these are already known. Burnett (*Quart. Reviews*, 1950, **4**, 290) has collected all the available data. We know that for styrene at 30°, $k_p = 135$ l. mol.$^{-1}$ sec.$^{-1}$, $k_{t_1} = 1{\cdot}7 \times 10^8$, and $k_p/k_{t_1} \simeq 10^6$, and this increases with higher temperature since the energy of activation of the termination reaction is comparatively small. In our experiments [C] has usually been less than 10^{-3}. We may justifiably assume k_p and k_i to be of the same order of magnitude, and k_{t_2} may have values of the same order of magnitude as k_{t_1}; k_i for benzoyl peroxide is of the order of 10^{-5} in the range 60—80° (Bartlett and Nozaki, *J. Amer. Chem. Soc.*, 1947, **69**, 2229; Cass, *ibid.*, 1946, **68**, 1976) in solvents like alcohol, Cellosolve, etc., where the speed of decomposition is inordinately high. Hence,

$$\alpha^2 = \frac{k_i[C]}{k_{t_1}} \cdot \frac{k_{t_2}^2}{k^2[M]^2} \simeq \frac{10^{-5} \times 10^{-3}}{1{\cdot}7 \times 10^8} \times \frac{1{\cdot}7 \times 10^8 \times 1{\cdot}7 + 10^8}{135 \times 135 \times [M]^2} \simeq \frac{10^{-2}}{[M]^2}$$

$< 0{\cdot}01$ under usual experimental conditions

This shows the small order of magnitude of α^2 and hence its comparatively small effect on $d[M]/dt$ under the usual experimental conditions, *i.e.*, from pure monomer to about 1 : 10 dilution. The generally observed square-root relation is also due in no small measure to the uncertainty of experimentally obtaining an accurate value of $d[M]/dt$.

We are also interested here in the relation of the molecular weight of the polymer formed by the two mechanisms. If we denote by M_1 the mean molecular weight produced by a

termination process t_1 alone, and consider the case where the polymerization rates are the same in both the cases, *i.e.*, where

$$(d[M]/dt)_1 = (d[M]/dt)_2 \text{ and so } [M^\bullet]_1 = [M^\bullet]_2$$

we shall have,

$$\frac{\overline{M}_1}{\overline{M}_2} = \frac{[V_{init.}]_2}{[V_{init.}]_1} = \frac{[V_{term.}]_2}{[V_{term.}]_1} = \frac{k_{t_1}[M^\bullet]_1^2 + k_1[R^\bullet]_1[M^\bullet]_1}{k_{t_1}[M^\bullet]_2^2} = 1 + \frac{k_{t_2}}{k_{t_1}} \cdot \frac{[R^\bullet]}{[M^\bullet]}$$

Hence, we see that $\overline{M}_1$ is generally greater than $\overline{M}_2$, as we found, and their ratio depends on the ratio k_{t_2}/k_{t_1}. It may also be pointed out that $[R^\bullet]$ and $[M^\bullet]$ are generally of the same order of magnitude, and so the above equation is not incompatible with our experimental observations as far as the order of magnitude goes.

Another explanation for the diminished termination rate is possible.† The efficiency of chain termination in the case of the persulphates is diminished by the mutual repulsion of the growing radicals, for the persulphates yield charged radicals and this factor reduces the chances of mutual termination to a great extent. This repulsive effect is absent in benzoyl peroxide-catalysed polymerization.

It should be pointed out that in the above discussion we have not taken into consideration the possibility that some proportion of the radicals produced by persulphates may be diradicals and consequently tend to produce longer chains; *e.g.*, oxygen might be formed by the decomposition of persulphate and might behave as diradicals and these may play some part in our case, producing longer chains and higher speed, but there is no experimental support for such a mechanism.

It has been demonstrated by Nozaki and Bartlett (*J. Amer. Chem. Soc.*, 1946, **68**, 1686) that the decomposition of benzoyl peroxide is not a simple unimolecular reaction but is complicated by the concurrent 1·5-molecular decomposition of the peroxide by the catalyst radical. This leads to a wastage of the benzoyl peroxide without helping the polymerization and, in fact, Redington (*J. Polymer Sci.*, 1948, **3**, 503) has introduced the concept of a wastage factor to explain the relative efficiency of the different acyl peroxides in initiating styrene polymerization. Cooper's observations (*Nature*, 1948, **162**, 897, 927) also confirm this. It is probable that, unlike the unstable organic peroxides, the inorganic persulphates are stable enough successfully to withstand the onslaught of their own free radicals owing either to the mutual repulsion or to their inherent stability, and thus are able to prevent such wastage : this would partly account for their observed superiority. However, the concept of wastage alone is not sufficient, for we have shown (*loc. cit.*) that the " wastage factor " is a conception which tends to reduce only the effective catalyst concentration and this alone would not explain the higher molecular weight in our case.

Our general conclusions are supported by observations made recently by Bartlett and Cotman (*J. Amer. Chem. Soc.*, 1949, **71**, 1419), who measured the rate of decomposition of potassium persulphate in aqueous methanol. They found that, although persulphates decompose according to a free-radical mechanism, the phenomenon of induced decomposition of persulphates by free radicals is practically absent. This is the opposite of what is observed with benzoyl peroxide.

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[*Received, April 10th*, 1951.]

† This was first suggested to the authors by Prof. Herman Mark in a private discussion.

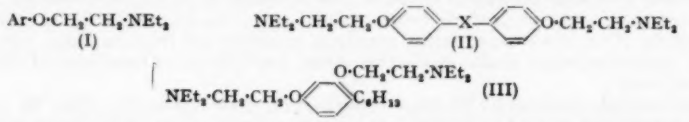
726. *Antituberculous Compounds. Part VIII.* Phenolic 2-Diethylaminoethyl Ethers and Analogues.*

By J. L. Lowe, D. A. Peak, and T. I. Watkins.

The observation by Chapman, Hager, and Shay (*J. Amer. Pharm. Assoc.*, 1947, **36**, 78) of the high activity, *in vitro*, of the bisdiethylaminoethyl ethers of stilbœstrol and hexylresorcinol has been extended by the preparation of a number of analogous bis- and mono-diethylaminoethyl ethers. Considerable simplification of the molecule is possible without loss of activity *in vitro*. As with the compounds examined by Chapman *et al.*, no activity *in vivo* could be observed.

Quinol monodiethylaminoethyl ether undergoes a novel type of disproportionation to quinol and the bis-ether.

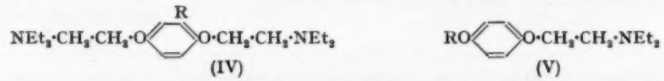
In Part I of this series (*J.*, 1949, 2680) it was noted that several 2-aryloxyethyldiethylamines (I) possessed appreciable activity *in vitro* against *Mycobacterium tuberculosis*. This activity was in most cases augmented by substitution of chlorine in the aryl group but this increase was seldom maintained in the presence of serum. The observation by Chapman *et al.* (*loc. cit.*) of



(I) (II) (III)

the high activity, *in vitro*, of 3 : 4-bis-*p*-2′-diethylaminoethoxyphenylhex-3-ene (bisdiethylaminoethyl ether of stilbœstrol) (II; X = CEt:CEt) and 1 : 3-bis-2′-diethylaminoethoxy-4-hexylbenzene (bisdiethylaminoethyl ether of hexylresorcinol) (III) suggested that two diethylaminoethoxy-groups might be necessary for the development of maximum activity in this type of compound. These two compounds were therefore prepared for examination, as well as the analogous hexœstrol ether (II; X = CHEt·CHEt). The high activities of these compounds *in vitro* were confirmed (see table) but, as already reported (Croshaw and Dickinson, *Brit. J. Pharm.*, 1950, **5**, 178), no activity could be detected *in vivo* for either the hexylresorcinol or the hexœstrol ether, the latter being chosen in preference to the stilbœstrol ether because of its slightly lower toxicity. This accords with the results in a later publication by Shay *et al.* (*J. Amer. Pharm. Assoc.*, 1948, **37**, 486). The present communication describes a number of related compounds, prepared for the purpose of elucidating the structural features governing activity and in the hope of obtaining a chemotherapeutically effective compound. Data concerning the compounds prepared are summarised in the accompanying table, together with their activities *in vitro*. Compounds were tested in all cases as their soluble hydrochlorides, directly prepared where necessary in solution from the free bases or from their derivatives.

Introduction of iodine into the hexœstrol ether (II; X = CHEt·CHEt) gave a tetraiodo-derivative of reduced activity, even with due allowance for the increased molecular weight. The occasional dyschemotherapeutic effect of halogen has already been noted in Part I (*loc. cit.*).



(IV) (V)

The simpler compounds, 4 : 4′-bis-2″-diethylaminoethoxydiphenyl and *p*-bis-2-diethylaminoethoxybenzene (quinol bisdiethylaminoethyl ether) (IV; R = H), showed the same high order of activity, particularly the latter, although again no activity could be detected *in vivo* (Croshaw and Dickinson, *loc. cit.*). That activity did not depend solely on the spatial separation of the two basic centres was shown by the inactivity of bis-*p*-2-diethylaminoethoxyphenyl sulphone (II; X = SO_2), a result in agreement with that of Shay *et al.* (*loc. cit.*). Further, the open-chain analogues, 1 : 8-bis-2′-diethylaminoethoxyoctane and bis-2-diethylaminoethyl ether were also inactive. The latter compound was first obtained as a by-product from the preparation

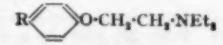
* Part VII, *J.*, 1951, 485.

of 1-2′-diethylaminoethoxy-4-ethoxybenzene (V; R = Et) but was obtained in better yield by the reaction of sodium diethylaminoethoxide with diethylaminoethyl chloride.

In contrast to *p*-bis-2-diethylaminoethoxybenzene, the corresponding resorcinol and catechol derivatives were virtually inactive. Since the introduction of a hexyl group into the resorcinol derivative converts it into the highly active 1 : 3-bis-2′-diethylaminoethoxy-4-hexylbenzene (4-hexylresorcinol bis-2-diethylaminoethyl ether) (III), it was thought that similar introduction of a hexyl group into the already active quinol compound (IV; R = H) might lead to a compound of exceptional activity. 2-Hexanoyl-1 : 4-dimethoxybenzene (hexanoylquinol dimethyl ether) was prepared by a modification of the method described by Cruickshank and Robinson (*J.*, 1938, 2066) for the preparation of 2-hydroxy-5-methoxyvalerophenone. It is noteworthy that in this case no demethylation of the quinol dimethyl ether occurred. This is probably due to the temperature of reaction, which in our case did not exceed room temperature, whereas Cruickshank and Robinson do not specify their final reaction temperature. Clemmensen reduction of the hexanoyl compound caused extensive resinification but there was successful reduction to 2-hexyl-1 : 4-dimethoxybenzene (hexylquinol dimethyl ether) by the Kishner method (cf. Nagami, *Ber.*, 1935, **68**, 1500). Demethylation and alkylation with diethylaminoethyl chloride gave the required 1 : 4-bis-2′-diethylaminoethoxy-2-hexylbenzene (2-hexylquinol bis-2-diethylaminoethyl ether) (IV; R = C_6H_{13}) which, however, proved to be less active than the unsubstituted compound (IV; R = H).

p-Bis-2-diethylaminoethylaminobenzene (VI), the nitrogen analogue of compound (IV; R = H), was prepared by alkylation of *NN′*-diformyl-*p*-phenylenediamine with diethylaminoethyl chloride and hydrolysis of the product. It proved to be of low activity.

(VI)



(VII)

A series of 4-alkoxy-1-2′-diethylaminoethoxybenzenes (V; R = alkyl) was next examined. The first method of preparation attempted was the alkylation of *p*-2-diethylaminoethoxyphenol (quinol mono-2-diethylaminoethyl ether) (V; R = H) in ethanolic sodium ethoxide with an excess of the alkyl halide. The main non-acidic products were *p*-dimethoxybenzene (quinol dimethyl ether) with methyl iodide, *p*-diethoxybenzene (quinol diethyl ether) with ethyl iodide, and *p*-bis-2-diethylaminoethoxybenzene (IV; R = H) with hexyl bromide. The formation of these products can be explained only by the assumption that the *p*-2-diethylaminoethoxyphenol undergoes disproportionation into the bis-ether and quinol. In the first two cases, the quinol has been dialkylated while the bis-ether has been lost as a water-soluble quaternary salt formed with the excess of alkyl iodide. In the third case, the much slower rate of quaternisation and alkylation by hexyl bromide (Menschutkin, *Z. physikal. Chem.*, 1890, **5**, 589) has permitted the isolation of the bis-ether as the sole basic product. The yield of bis-ether in this case corresponded to a 90% disproportionation. In the other two cases the yields of quinol dialkyl ethers correspond to a 75% and 96% disproportionation respectively. Under the same conditions, in the absence of an alkylating agent, an amount of the bis-ether corresponding to a 45% disproportionation was isolated. The disproportionation is not reversible since, when an equimolecular mixture of the bis-ether and quinol was treated under the same conditions, a careful examination of the product failed to reveal any of the mono-ether.

The mechanism of the disproportionation has not been investigated, but it clearly involves the diethylamino-group since no such disproportionation could be detected with simple monoalkyl ethers of quinol. No close analogies of this facile trans-etherification appear to exist. Ipatieff and Burwell (*J. Amer. Chem. Soc.*, 1941, **63**, 969) have observed the interconversion of simple and mixed ethers but only under conditions of high-temperature catalysis. Other examples of trans-etherification, *e.g.*, of ethyl ββ-diethoxypropionate and ethyl αα-diethoxysuccinate with alcohols (Croxall *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 2736, 2741; 1950, **72**, 4274) and of alkyl β-alkoxypropionates with higher alcohols in the presence of sodium methoxide (Seeger, U.S.P. 2,293,000), are not analogous because of the special molecular environment of the ether groups in these cases.

The alternative route from the quinol monoalkyl ether and diethylaminoethyl chloride proved more successful. The usual conditions of condensation in boiling ethanol gave poor results, but condensation at room temperature in aqueous sodium hydroxide solution afforded satisfactory yields. The methoxy- and ethoxy-compounds (V; R = Me and Et, respectively) were of low activity but in the case of the butoxy- and the octyloxy-compound (V; R = C_4H_9 and C_8H_{17}, respectively) activity was restored to a level comparable with that of

p-bis-2-diethylaminoethoxybenzene. The second diethylaminoethyl group seems therefore to be exerting only a mass effect equally well provided by a simple alkyl group. Both diethylaminoethyl groups cannot be replaced, since *p*-dihexyloxybenzene (quinol dihexyl ether) is of very low activity.

Confirmation of this effect was found in a series of 4-alkyl-1-2′-diethylaminoethoxybenzenes (VII; R = Me, Pr, and C_6H_{13}, respectively), where the hexyl compound was highly active. 3 : 5-Dichloro-4-2′-diethylaminoethoxytoluene, 3 : 5-dichloro-2-2′-diethylaminoethoxytoluene, and 2 : 6-dichloro-1-2′-diethylaminoethoxy-4-hexylbenzene were also prepared. The last compound provided a further example of the occasional dyschemotherapeutic effect of chlorine.

Finally, a branched-chain analogue of compound (VII; R = C_6H_{13}) was prepared by reaction of *p*-2-diethylaminoethoxypropiophenone (VII; R = EtCO) with propylmagnesium bromide to give 1-2′-diethylaminoethoxy-4-(1-ethyl-1-hydroxy-*n*-butyl)benzene [VII; R = EtPrC(OH)] and dehydrating this to the unsaturated compound in which the position of the ethylenic linkage was not determined. Catalytic reduction afforded 1-2′-diethylaminoethoxy-4-(1-ethyl-*n*-butyl)benzene (VII; R = CHEtPr). This compound, which contains the partial skeleton of the hexœstrol ether (II; X = CHEt·CHEt), although highly active in the absence of serum, was almost inactivated by its presence; comparison with the isomeric compound (VII; R = C_6H_{13}) provides a further example of the unpredictability of the serum effect. The intermediate compound [VII; R = EtPrC(OH)] was less affected but no activity could be observed *in vivo* (Croshaw and Dickinson, *loc. cit.*).

Experimental.

Preparation of Phenolic Intermediates.

Known phenolic intermediates were prepared by the following methods: 4 : 4′-dihydroxydiphenyl (Hirsch, *Ber.*, 1889, **22**, 335); *p*-methoxyphenol (Robinson and Smith, *J.*, 1926, 393); *p*-ethoxy-, *p*-butoxy-, and *p*-octyloxy-phenol (Klarmann, Gatyas, and Schternov, *J. Amer. Chem. Soc.*, 1932, **54**, 298); 3 : 5-dichloro-4-hydroxytoluene (Zincke, *Annalen*, 1903, **328**, 278); 3 : 5-dichloro-2-hydroxytoluene (Claus and Riemann, *Ber.*, 1883, **16**, 1601); *p*-propylphenol (Clemmensen, *Ber.*, 1914, **47**, 53); *p*-hexylphenol (Coulthard, Marshall, and Pyman, *J.*, 1930, 280); and 2 : 6-dichloro-4-hexylphenol (U.S.P. 2,176,010), b. p. 121—125°/0·75 mm. (Found: C, 57·6; H, 6·8. Calc. for $C_{12}H_{14}OCl_2$: C, 58·3; H, 6·5%).

3 : 4-*Bis*-(4-*hydroxy*-3 : 5-*di*-*iodophenyl*)*hexane* (3 : 3′ : 5 : 5′-*Tetraiodohexœstrol*).—A solution of iodine (20·3 g., 8 atoms) in aqueous potassium iodide solution was added during 1 hour to a solution of hexœstrol (5·4 g., 1 mol.) in 0·5N-potassium hydroxide (320 c.c.). Stirring was continued for a further hour, and a little sodium hydrosulphite (dithionite) added to discharge the purplish colour of the solution. The product was isolated by salting out the potassium salt with 10N-potassium hydroxide (50 c.c.). This was filtered off, washed with 2N-potassium hydroxide, and dissolved in water, and the free *phenol* precipitated with sulphur dioxide. Crystallisation from ethyl acetate afforded the product as flat needles (10·5 g.), m. p. 239·5—240° (decomp.) (Found: C, 28·4; H, 2·3. $C_{18}H_{18}O_2I_4$ requires C, 27·9; H, 2·3%). (Prepared by Mr. P. Oxley.)

Hexylquinol.—Hexanoyl chloride (49 g.) was added to a suspension of powdered aluminium chloride (53 g., 1·1 mols.) in pure carbon disulphide (100 c.c.). The mixture was warmed on the steam-bath until all the solid had dissolved, two layers being formed. It was then cooled in a freezing-mixture, and a solution of quinol dimethyl ether (50 g., 1 mol.) in carbon disulphide (200 c.c.) was added during 1 hour with shaking. The mixture was then allowed to attain room temperature during which time hydrogen chloride was steadily evolved. After 21 hours, the dark oily complex which had separated was decomposed by pouring the mixture on dilute hydrochloric acid and ice. The solvent layer was separated, dried ($MgSO_4$), and concentrated. Distillation gave unchanged quinol dimethyl ether (25 g.; b. p. 70—72°/1 mm.) and then 2-*hexanoyl*-1 : 4-*dimethoxybenzene* (*hexanoylquinol dimethyl ether*) (38 g.; b. p. 132—134°/0·5 mm.) (Found: C, 71·4; H, 8·7. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%). It slowly solidified to rod-like crystals, m. p. *ca.* 15°. It gave a transient blue followed by a permanent green colour with alcoholic ferric chloride. It was insoluble in sodium hydroxide solution.

A mixture of the above material (28 g.) with absolute ethanol (28 c.c.) and 82% hydrazine hydrate (14 g.) was heated under reflux for 2½ hours, and the ethanol removed *in vacuo*. The residue was heated to 150° in an oil-bath and finely powdered potassium hydroxide (56 g.) was added in one portion. Vigorous evolution of nitrogen ensued and continued for ½ hour. The temperature was then raised for a short time to 170°. The cooled melt was diluted with water (75 c.c.), and the resultant oil isolated with ether. Distillation afforded 2-*hexyl*-1 : 4-*dimethoxybenzene* (2-*hexylquinol dimethyl ether*) (16·5 g.), b. p. 87—96°/0·1 mm. (mainly at 90—94°) (Found: C, 75·3; H, 9·6. $C_{14}H_{22}O_2$ requires C, 75·7; H, 9·9%).

The foregoing compound (5·25 g.) was heated under reflux for 2 hours with 48% hydrobromic acid (50 c.c.), and the resultant oil isolated with ether. Distillation of the product gave *hexylquinol* (3·18 g.), b. p. 152°/1 mm., small needles (from light petroleum–benzene), m. p. 88° (Found: C, 74·1; H, 9·9. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%).

p-2-*Diethylaminoethoxyphenol*.—This is a known compound (Bovet, *Arch. intern. Pharmacodyn.*, 1937, **56**, 33; Vallery-Radot, *Compt. rend. Soc. biol.*, 1943, **137**, 296) but its preparation and properties do not appear to have been described. Quinol (44 g.) was dissolved in an ice-cold solution of sodium

hydroxide (40 g.) in water (280 c.c.) under nitrogen. Diethylaminoethyl chloride (54·2 g., 1 mol.) was added, and the mixture shaken vigorously for 16 hours, and finally heated at 100° for 2 hours to complete the reaction. The solution was cooled, acidified with sulphuric acid, and unchanged quinol extracted with ether (2 × 400 c.c.). The aqueous layer was adjusted to pH 10 with sodium hydroxide, and the product isolated with ether (2 × 500 c.c.). Distillation gave *p*-2-diethylaminoethoxyphenol (43·7 g.), b. p. 161°/2 mm., m. p. 81°. Its *picrate* separated from ethanol in yellow needles, m. p. 129° (Found: C, 49·5; H, 5·1. $C_{18}H_{22}O_9N_4$ requires C, 49·3; H, 5·0%).

Disproportionation of p-2-*Diethylaminoethoxyphenol.*—(*a*) This phenol (5·23 g.) and methyl iodide (7·1 g., 2 mols.) were added to a solution of sodium (0·575 g., 1 mol.) in absolute ethanol (50 c.c.), and the mixture was heated under reflux for 48 hours. Removal of the ethanol *in vacuo*, addition of water to the residue, and extraction with ether furnished a solid (1·3 g.), m. p. 50°, identified by mixed m. p., after recrystallisation, as quinol dimethyl ether. This corresponds to a 75% disproportionation of the diethylaminoethoxyphenol. Similarly, ethyl iodide gave quinol diethyl ether (2·0 g.), m. p. 66°, corresponding to a 96% disproportionation.

(*b*) Attempted alkylation with hexyl bromide as above afforded a liquid product (3·5 g.), b. p. 174°/2 mm., identified by formation of its picrate, m. p. 183—184° (Found: N, 14·7; Calc. for $C_{26}H_{34}O_{16}N_8$: N, 14·6%), as *p*-bis-2-diethylaminoethoxybenzene (see table, compound 6). This corresponds to a 90% disproportionation.

(*c*) *p*-2-Diethylaminoethoxyphenol (10·45 g.) and a solution of sodium (1·15 g.) in absolute ethanol (50 c.c.) were heated under reflux for 16 hours. The ethanol was removed *in vacuo*, the residue dissolved in water, and the solution made strongly alkaline with sodium hydroxide. Extraction with ether yielded an oily base (3·5 g.), identified as its picrate, m. p. 183—184° undepressed by *p*-bis-2-diethylaminoethoxybenzene picrate. This corresponds to a 45% disproportionation.

Preparation of Diethylaminoethyl Derivatives.

The following general methods were used as indicated in the table.

Method A.—Sodium (1 atom for each phenolic group) was dissolved in absolute ethanol, and the phenol and diethylaminoethyl chloride (1—1·2 mols. for each phenolic group) were added. The solution was refluxed with stirring for 1—10 hours (depending on the rate of separation of sodium chloride), the ethanol removed *in vacuo*, and water added. The oil was isolated with ether and purified either by distillation or by direct conversion into the hydrochloride or other derivative.

Method B.—The phenol was dissolved in 3·5N-sodium hydroxide (2·5 equivs.) and shaken at room temperature with diethylaminoethyl chloride (3—4 mols.) for 16—60 hours. The mixture was then made strongly alkaline with sodium hydroxide and extracted with ether. The product was isolated as in method A.

Method C.—The phenol was dissolved in methanol containing sodium methoxide (1 equiv.), and benzene added. The methanol was removed azeotropically, diethylaminoethyl chloride (1 mol.) added to the benzene suspension of the sodium salt, and the mixture heated under reflux for 24 hours. The benzene solution was washed with dilute aqueous sodium hydroxide, and the product extracted into dilute hydrochloric acid. The free base, isolated with ether after basification, was purified by distillation or as a derivative.

1 : 8-*Bis*-2′-*diethylaminoethoxyoctane.*—Sodium (1·7 g.) was dissolved in diethylaminoethanol (100 c.c.), and 1 : 8-dibromo-octane (10·0 g.) added. A white precipitate formed almost immediately. The mixture was heated at 100° overnight with stirring, and filtered, and the diethylaminoethanol removed *in vacuo*. The residual oil was dissolved in ether, the solution filtered, and the product fractionated through a short Vigreux column. The crude distillate (b. p. 140—180°/2 mm.) still contained bromine and was therefore reheated with diethylaminoethanol containing dissolved sodium. Again isolated as before, the product was bromine-free but still boiled over a wide range (120—160°/2 mm.), probably owing to superheating. A middle cut gave a correct analysis for the desired compound (see table).

Bis-2-*diethylaminoethyl Ether.*—Sodium (2·3 g.) was dissolved in warm diethylaminoethanol (50 c.c.), and diethylaminoethyl chloride (16·9 g., 1·25 mols.) added. The mixture was kept at room temperature for 2 days and then heated under reflux for 2 hours. Distillation of the filtered solution gave bis-2-diethylaminoethyl ether (see table). This compound was identical (m. p. and mixed m. p. of picrate) with the by-product obtained in 16% yield during the alkylation of *p*-ethoxyphenol with diethylaminoethyl chloride by method B above.

p-*Bis*-2-*diethylaminoethylaminobenzene.*—*NN′*-Diformyl-*p*-phenylenediamine (4·1 g.) (Wundt, *Ber.*, 1878, **11**, 828) was dissolved in a mixture of acetone (100 c.c.) and methanol (10 c.c.). Diethylaminoethyl chloride (13·55 g., 4 mols.) and an excess of potassium carbonate (10 g.) were added, and the mixture was heated under reflux with stirring for 5 hours. Solvents and low-boiling components were removed up to 100°/1—2 mm., and the residual oil was hydrolysed by heating it under reflux with 5N-hydrochloric acid (30 c.c.) for 2 hours. The solution was then cooled and basified, and the oil isolated with ether. Distillation gave *p*-bis-2-diethylaminoethylaminobenzene (see table).

p-*Dihexyloxybenzene* (*Quinol Dihexyl Ether*).—Quinol (5·5 g., 1 mol.) and hexyl bromide (20·6 g., 2·5 mols.) were added to a solution of potassium hydroxide (5·6 g., 2 mols.) in ethanol (50 c.c.), and the solution was heated under reflux for 3 hours. On cooling, p-*dihexyloxybenzene* (*quinol dihexyl ether*) (8 g.; m. p. 41—43°) separated. A further small crop (0·36 g.; m. p. 36°), together with a small amount of unchanged quinol, was obtained by evaporation of the filtrate. The product crystallised from methanol in plates, m. p. 45° (Found: C, 77·7; H, 10·85. $C_{18}H_{30}O_2$ requires C, 77·7; H, 10·8%).

Compound	Activity: * in absence of serum	Activity: * in presence of 10% serum	Method and yield, %	B. p. of base	Derivative	Solvent	Crystal form	M. p.	Formula	N, % Found	N, % Reqd.
(1) 3 : 4-Bis-*p*-2′-diethylamino-ethoxyphenylhex-3-ene	100 (10,000)	100 (500)	A, 49·5	—	Dihydro-chloride	EtOAc–EtOH	Needles	236°	$C_{30}H_{46}O_2N_2Cl_2$	5·0	5·2
(2) 1 : 3-Bis-2′-diethylamino-ethoxy-4-hexylbenzene	50—100	50—100	A, 25	183—187°/ 0·4 mm.	—	—	—	—	$C_{34}H_{44}O_2N_2$	7·0	7·1
(3) 3 : 4-Bis-*p*-2′-diethylamino-ethoxyphenylhexane	1000 (10,000)	100 (500)	A, 46	—	*Dihydro-chloride*	EtOAc–EtOH	Needles	222	$C_{30}H_{50}O_2N_2Cl_2$	5·15	5·2
(4) 3 : 4-Bis-(4-2′-diethylamino-ethoxy-3 : 5-di-iodo-phenyl)hexane	50—100	5—10	A, 35	—	*Dihydro-chloride*	EtOH	Needles	241	$C_{30}H_{46}O_2N_2Cl_2I_4$	2·9	2·7
(5) 4 : 4′-Bis-2″-diethylamino-ethoxydiphenyl	500	10—100	A, 38·5	—	*Dihydro-chloride*	EtOAc–EtOH	Needles	235	$C_{24}H_{36}O_2N_2Cl_2$	6·0	6·1
(6) *p*-Bis-2-diethylamino-ethoxybenzene	100—500	100	B, 47	182—183°/ 3 mm.	Dipicrate	EtOH	Rods	184	$C_{30}H_{36}O_{16}N_8$	14·7	14·6
(7) Bis-*p*-2′-diethylamino-ethoxyphenyl sulphone	1	—	A, 29	—	*Direineckate dihydrate*	30% $COMe_2$	Needles	130 †	$C_{32}H_{54}O_6N_{14}S_2Cr_2$	17·1	17·5
					Direineckate	—	—	165 †	$C_{32}H_{50}O_4N_{14}S_2Cr_2$	18·0	18·05
(8) 1 : 8-*Bis-2′-diethylamino-ethoxyoctane*	1	—	See p. 3289	140°/3 mm.	—	—	—	—	$C_{20}H_{44}O_2N_2$	8·25	8·1
(9) *Bis-2-diethylaminoethyl ether*	<1	—	See p. 3289	85°/0·5 mm.	—	—	—	—	$C_{12}H_{28}ON_2$	12·9	13·0
					Dipicrate	EtOH	Needles	132·5	$C_{24}H_{24}O_{15}N_8$	16·9	16·6
(10) *m*-Bis-2-diethylamino-ethoxy benzene	—	<1 (1)	B, 21	178°/0·15 mm.	—	—	—	—	$C_{18}H_{32}O_2N_2$	9·35	9·1
(11) *o*-Bis-2-diethylamino-ethoxybenzene	—	1	B, 44	160°/1·5 mm.	—	—	—	—	$C_{18}H_{32}O_2N_2$	9·1	9·1
(12) 1 : 4-Bis-2′-diethylamino-ethoxy-2-hexylbenzene	—	50	B, 71·5	169°/0·3 mm.	*Dipicrate*	MeOH	Prisms	125·5	$C_{36}H_{50}O_{16}N_8$	13·45	13·2
(13) p-*Bis-2-diethylaminoethyl-aminobenzene*	5—10	5 (10)	See p. 3289	180°/1 mm.	—	—	—	—	$C_{16}H_{34}N_4$	18·1	18·3
(14) 1-2′-Diethylaminoethoxy-4-methoxybenzene	5—10	1—5	B, 29	127—130°/ 3 mm.	*Picrate*	EtOH	Rods	110	$C_{19}H_{24}O_9N_4$	12·6	12·4
(15) 1-2′-*Diethylaminoethoxy-4-ethoxybenzene*	5	5	B, 71	183—186°/ 5 mm.	—	—	—	—	$C_{14}H_{23}O_2N$	6·1	5·9
					Picrate	EtOH	Needles	77—78	$C_{20}H_{26}O_9N_4$	—	—
(16) 4-*Butoxy*-1-2′-*diethylamino-ethoxybenzene*	100	50	B, 45	128°/0·5 mm.	—	—	—	—	$C_{16}H_{27}O_2N$	5·3	5·3

(17) 1-2′-*Diethylaminoethoxy*-4-*octyloxybenzene*	100	10—50	B, 54·5	190°/1·3 mm.	—	—	—	—	$C_{30}H_{51}O_2N$	4·4	4·4
(18) p-*Dihexyloxybenzene*	—	1 (10)	See p. 3289	—	—	MeOH	Plates	45	$C_{18}H_{30}O_2$	—	—
(19) *p*-2′-Diethylaminoethoxytoluene	10	—	A, 72	—	*Hydrochloride*	EtOH–Et_2O	Fine needles	107	$C_{13}H_{22}ONCl$	5·7	5·7
(20) 3 : 5-*Dichloro*-4-2′-*diethylaminoethoxytoluene*	10	10	C, 56	114—117°/1 mm.	—	—	—	—	$C_{13}H_{19}ONCl_2$	5·3	5·1
					Picrate	C_6H_6	Needles	155—156	$C_{19}H_{22}O_8N_4Cl_2$	11·0	11·1
(21) 3 : 5-Dichloro-2-2′-diethylaminoethoxytoluene	10	10	C, 79	132—134°/2 mm.	*Hydrochloride*	EtOH	Needles	153—154	$C_{13}H_{20}ONCl_3$	4·6	4·5
(22) 1-2′-Diethylaminoethoxy-4-propylbenzene	100	10	A, 90	—	*Hydrochloride*	EtOAc–EtOH	Needles	141—142	$C_{13}H_{20}ONCl$	5·2	5·15
(23) 1-2′-*Diethylaminoethoxy*-4-*hexylbenzene*	100	100	A, 75	140°/0·5 mm.	—	—	—	—	$C_{18}H_{31}ON$	5·0	5·05
(24) 2 : 6-*Dichloro*-1-2′-*diethylaminoethoxy*-4-*hexylbenzene*	10	10	A, 61	167—171°/1 mm.	—	—	—	—	$C_{18}H_{29}ONCl_2$	4·05	4·0
(25) 4-2′-Diethylaminoethoxypropiophenone	5	—	A, 64	152°/1 mm.	*Hydrochloride*	EtOAc–EtOH	Needles	149—150	$C_{15}H_{24}O_2NCl$	5·0	4·85
(26) 1-2′-Diethylaminoethoxy-4-(1-ethyl-1-hydroxy-*n*-butyl)benzene	50—100	50	See p. 3292	—	*Hydrochloride*	EtOAc	Needles	130—131	$C_{18}H_{32}O_2NCl$	4·4	4·25
(27) 1-2′-Diethylaminoethoxy-4-(1-ethyl-*n*-but-1-enyl)-benzene	1000	50—100	See p. 3292	—	*Hydrochloride*	EtOAc	Needles	144	$C_{18}H_{30}ONCl$	4·7	4·5
(28) 1-2′-Diethylaminoethoxy-4-(1-ethyl-*n*-butyl)benzene	500—1000	10	See p. 3292	—	*Hydrochloride*	$COMe_2$	Needles	157—158	$C_{18}H_{32}ONCl$	4·7	4·5

* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating pellicle method) (Croshaw and Dickinson, *loc. cit.*). Figures in parentheses represent dilutions at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

† With decomposition.

Notes to table.

(1) Chapman *et al.* (*loc. cit.*) record m. p. 236—237° (slight decomp.). (2) Picrate, m. p. 108—109°. Chapman *et al.* (*loc. cit.*), who use a considerable deficiency of 2-diethylaminoethyl chloride, record b. p. 220—225°/11 mm. for the base contaminated with appreciable amounts of monoether, and m. p. 108—109·5° for the picrate. (6) Found for the dipicrate: C, 46·4; H, 4·6. Calc. for $C_{30}H_{33}O_{16}N_9$: C, 47·0; H, 5·0%. Protiva, Jilek, Kolinsky, Rericha, and Urban (*Coll. Czech. Chem. Comm.*, 1948, **13**, 1326) record b. p. 178—182°/1—2 mm. for the base and m. p. 184—185° for the dipicrate. (7) Found for the *dihydrate*: H_2O, 2·7. $C_{28}H_{50}O_4N_{16}S_2Cr_2.2H_2O$ requires H_2O, 3·2%. (8) Prepared by Mr. F. F. Whitmont. (9) Found for the *dipicrate*: C, 43·0; H, 4·9. $C_{44}H_{54}O_{16}N_8$ requires C, 42·7; H, 5·0%. (10) and (11) Protiva *et al.* (*loc. cit.*) record b. p. 194—200°/5 mm. and b. p. 165—175°/1—3 mm., respectively. (14) Found: C, 50·7; H, 5·7. $C_{19}H_{24}O_2N_4$ requires C, 50·45; H, 5·3%. (20) and (21) Prepared by Mr. F. F. Whitmont. (24) Prepared by Mr. D. J. Drain. A solid hydrochloride or picrate could not be prepared. (27) Found: C, 69·4; H, 9·2. $C_{18}H_{29}ONCl$ requires C, 69·3; H, 9·6%. (28) Found: C, 68·7; H, 10·0. $C_{18}H_{32}ONCl$ requires C, 68·9; H, 10·2%.

1-2′-*Diethylaminoethoxy*-4-(1-*ethyl*-1-*hydroxy*-n-*butyl*)*benzene* (**3-p-2′-*Diethylaminoethoxyphenylhexan*-2-*ol*).**—A solution of *p*-2-diethylaminoethoxypropiophenone (16 g.) in anhydrous ether (50 c.c.) was added slowly to a Grignard solution prepared from magnesium turnings (1·62 g., 1·1 atoms) and propyl bromide (8·3 g., 1·1 mols.) in ether (40 c.c.). The resulting green suspension was then heated under reflux for 45 minutes, and poured into a mixture of ice and hydrochloric acid. The aqueous phase was brought nearly to neutrality with sodium hydroxide solution and then excess of solid sodium hydrogen carbonate was added. The ethereal layer was separated, and the product isolated by distillation as a colourless oil, b. p. 146—151°/0·3 mm. The crude material was probably a mixture of the carbinol and its dehydration product, since a pure hydrochloride (see table) was obtained only by repeated fractional crystallisation.

1-2′-*Diethylaminoethoxy*-4-(1-*ethyl*-n-*but*-1-*enyl*)*benzene* (**3-p-2′-*Diethylaminoethoxyphenylhex*-3-*ene*).**—The foregoing crude product (15 g.) was boiled under reflux with 98% formic acid (50 g.) for 45 minutes. Most of the formic acid was removed *in vacuo*, and the free base isolated with sodium hydroxide and ether. The crude product (13·5 g.; b. p. 144—148°/0·9 mm.) still contained oxygenated impurities. It was purified by redistillation over sodium (2·0 g.), and the distillate (10·8 g.; b. p. 140—142°/0·7 mm.) converted into the hydrochloride (see table).

1-2′-*Diethylaminoethoxy*-4-(1-*ethyl*-n-*butyl*)*benzene* (**3-p-2′-*Diethylaminoethoxyphenylhexane*).**—The foregoing unsaturated base (8·2 g.) in methanol (80 c.c.) was hydrogenated at atmospheric pressure and temperature with Raney nickel catalyst. Absorption of the theoretical amount of hydrogen was rapid. Isolated in the usual manner, the product distilled at 135°/0·5 mm. (7·3 g.) and was further purified by conversion into its hydrochloride (see table).

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[*Received, May 29th,* 1951.]

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727. *Antituberculous Compounds. Part IX.* Some Dialkylaminoalkyl Sulphones and Related Compounds.*

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A number of alkyl 2-diethylaminoethyl sulphones have been prepared, together with related compounds in which the sulphonyl group was replaced by other atoms or groups. Of these the sulphides are outstandingly active *in vitro*. Some aminomethyl sulphones of the type *p*-Me·C_6H_4·SO_2·CH_2·NRR′ were also prepared. The corresponding alkyl aminomethyl sulphones appear to be too unstable to exist.

In the course of the preparation of amino-substituted Bunte salts, an interesting difference in the behaviour of 2-diethylamino- and 2-dioctylamino-ethyl chlorides was observed.

MANY aliphatic amines, particularly those containing 16—20 carbon atoms, possess marked activity *in vitro* against *Mycobacterium tuberculosis* (Stanley, Coleman, Greer, Sacks, and Adams, *J. Pharmacol.*, 1932, **45**, 121; Borrows, Hargreaves, Page, Resuggan, and Robinson, *J.*, 1947, 197) but are inactive *in vivo*. Many aromatic amines also show a high degree of activity *in vitro* (*e.g.*, Bloch, Lehr and Erlenmeyer, *Helv. Chim. Acta*, 1945, **28**, 1406), but activity *in vivo* is shown only by compounds of the diaminodiphenyl sulphone type which contain a sulphone group in addition to the amino-groups. It therefore appeared of interest to examine the effect of the introduction of sulphonyl groups into aliphatic amines. The

NEt_2·CH_2·CH_2·XR (I) $\quad$ Me·N(CH_2·CH_2·SO_2·C_8H_{17})$_2$ (II) $\quad$ Pr·CH(S·CH_2·CH_2·NEt_2)$_2$ (III)

alkyl 2-diethylaminoethyl sulphones (I; X = SO_2, R = Bu, C_8H_{17}, and $C_{16}H_{33}$) were prepared by the oxidation of the corresponding sulphides (I; X = S). Methylbis-2-octylsulphonylethylamine (II) was similarly prepared as an example of an amine with two β-sulphonyl groups. The activities *in vitro* of these sulphones, recorded in the experimental section, were of a low order. The intermediate sulphides (I; X = S), however, showed high activity. The single sulphoxide prepared, 2-diethylaminoethyl octyl sulphoxide (I; X = SO, R = C_8H_{17}), was intermediate in activity between the corresponding sulphide and sulphone.

* Part VIII, preceding paper.

Several isosteric analogues of the sulphides were accordingly prepared in which replacement of the sulphur atom by other atoms or groups would afford some measure of the specific effect of the sulphur atom on antituberculous activity. The following compounds were prepared by standard procedures: (1) butyl 2-diethylaminoethyl ether and 2-diethylaminoethyl octyl ether as oxygen analogues, (2) diethylheptylamine and diethylundecylamine as methylene analogues, and (3) 2-diethylaminoethyl nonyl ketone as a carbonyl analogue. All showed reduced activity. The specificity of the sulphur in the β-position to the diethylamino-group was further shown by the preparation of 3-diethylaminopropyl propyl sulphide (I; X = CH_2·S, R = Pr) which was much less active than the isomeric butyl 2-diethylaminoethyl sulphide (I; X = S, R = Bu). Butaldehyde bis-2-diethylaminoethyl mercaptal (III) was prepared by condensation of either butaldehyde and 2-diethylaminoethanethiol hydrochloride or 1 : 1-dichlorobutane and sodium 2-diethylaminoethyl sulphide but the second 2-diethylaminoethyl sulphide residue had an adverse effect on activity.

As further types of basic sulphones, bis-2-diethylaminoethyl sulphone and *p*-aminophenyl 2-diethylaminoethyl sulphone were prepared. Neither proved to be of interest. The sulphide and sulphoxide corresponding to the former were also ineffective. The disulphide showed slight activity.

p-Me·C_6H_4·SO_2·CH_2R (IV) RS·SO_2·ONa (V) RS·SO_2·OR (VI)

A few α-amino-sulphones were prepared by condensation of hydroxymethyl *p*-tolyl sulphone (IV; R = OH) (Meyer, *J. pr. Chem.*, 1901, **63**, 168) with various amines. In this way *N*-methyl-*N*-(toluene-*p*-sulphonylmethyl)aniline (IV; R = NMePh), 4-(toluene-*p*-sulphonylmethyl)morpholine (IV; R = N<[CH_2]$_4$>O), *N*^{4}-(toluene-*p*-sulphonylmethyl)sulphanilamide (IV; R = NH·C_6H_4·SO_2·NH_2-*p*) and 2-methyl-5-(toluene-*p*-sulphonylmethylamino)-1 : 3 : 4-oxadiazole (IV; R = NH·C:N·N:CMe, O) were obtained. These compounds were inactive and unstable, readily evolving formaldehyde when warmed with dilute acid. The failure to isolate anything but fission products by oxidation of diethylaminomethyl methyl sulphide (cf. McLeod and Robinson, *J.*, 1921, **119**, 1470), under the mildest possible conditions, indicates that alkyl diethylaminomethyl sulphones are even less stable.

A few compounds of the Bunte salt type were also prepared. 2-Diethylaminoethyl bromide or chloride condensed readily with sodium thiosulphate to give the monoester sodium salt (V; R = CH_2·CH_2·NEt_2). No tendency could be detected, even in the presence of a large excess of the halide, for the formation of any diester (VI; R = CH_2·CH_2·NEt_2). It was, therefore, surprising to find that with 2-dioctylaminoethyl chloride the sole product was the diester [VI; R = CH_2·CH_2·N(C_8H_{17})$_2$], half the sodium thiosulphate remaining unchanged when equivalent quantities of the reactants were used. This appears to be the first diester of thiosulphuric acid to have been described.

The preparation of sodium octyl and hexadecyl thiosulphates (V; R = C_8H_{17} and $C_{16}H_{33}$) is also described, since these have been found convenient sources of the corresponding thiols which are readily obtained by acid hydrolysis (cf. Westlake and Dougherty, *J. Amer. Chem. Soc.*, 1941, **63**, 658; 1942, **64**, 149). Sodium butyl thiosulphate (V; R = Bu), hydrolysed without isolation, is a less favourable source of butanethiol.

The highly active butyl 2-diethylaminoethyl sulphide (I; X = S, R = Bu) was selected for trial *in vivo* in guinea-pigs but no activity could be detected (Croshaw and Dickinson, *Brit. J. Pharmacol.*, 1950, **5**, 178).

Experimental.

The activities recorded refer to the standard conditions detailed on p. 3291 (footnote *). The symbol (*s*) indicates that the inhibition is in the presence of 10% serum.

Sodium Octyl Thiosulphate.—A solution of sodium thiosulphate (25 g.) in water (110 c.c.) was added to octyl bromide (20 g., 1 mol.) and ethanol (110 c.c.). The mixture was heated under reflux for 3½ hours, by which time it was homogeneous and sodium thiosulphate could no longer be detected. The ethanol was removed under diminished pressure, finally over sulphuric acid. The residual solid was extracted with hot acetone. On cooling, the extract deposited *sodium octyl thiosulphate monohydrate* in plates (16 g.), further purified by recrystallisation from ethanol (Found: H_2O, 6·7. $C_8H_{17}O_3S_2Na,H_2O$ requires H_2O, 6·7%) (activity = <1). Drying at 40° *in vacuo* over phosphoric oxide afforded the anhydrous *salt* (Found: S, 25·6; Na, 9·1. $C_8H_{17}O_3S_2Na$ requires S, 25·8; Na, 9·3%).

Sodium Hexadecyl Thiosulphate.—A mixture of hexadecyl iodide (7·0 g.), sodium thiosulphate (5·0 g., 1 mol.), ethanol (15 c.c.), and water (11 c.c.) was heated under reflux until it became homogeneous

(3 hours). On cooling, the product separated in translucent plates as a *dihydrate* (5·9 g.) and was recrystallised from ethanol (Found : S, 16·5; Na, 5·7; H_2O, loss *in vacuo* at 70°, 10·0. $C_{16}H_{32}O_2S_2Na_2,2H_2O$ requires S, 16·2, Na, 5·8; H_2O, 9·1%).

Sodium 2-Diethylaminoethyl Thiosulphate.—2-Diethylaminoethyl bromide hydrobromide (20 g., 1 mol.), N-sodium hydroxide (76·6 c.c., 1 equiv.), and sodium thiosulphate (19 g., 1 mol.) were stirred together at 35—40°, and the reaction was followed by titration of 3-c.c. aliquots with 0·1N-iodine at intervals. Reaction was almost complete after 20 minutes. The solution was evaporated to dryness *in vacuo*, and the residue extracted with hot acetone. The extract, on cooling, deposited *sodium 2-diethylaminoethyl thiosulphate* as plates, further purified by crystallisation from ethanol (yield, 11·8 g.) (Found : N, 5·8. $C_6H_{14}O_3NS_2Na$ requires N, 5·95%) (activity <1). The product decomposed appreciably at 100°. The same compound was obtained by using diethylaminoethyl chloride but the reaction was slower.

Bis-2-dioctylaminoethyl Thiosulphate.—2-Dioctylaminoethyl chloride hydrochloride (4·8 g.) (Part I, *J.*, 1949, 2680) was dissolved in ethanol (12 c.c.), and 0·1N-sodium hydroxide (13·95 c.c., *i.e.*, almost 1 equiv.) added to give a solution neutral to phenolphthalein. A solution of sodium thiosulphate (3·5 g., 1 mol.) in water (7 c.c.) was then added, and the two-phase mixture stirred at room temperature. At intervals, aliquots (1 c.c.) of the lower, aqueous layer were titrated with 0·01N-iodine. The titre fell steadily during 8 hours to 50% of its original value where it remained constant. The same result was obtained at temperatures as varied as 0° and 75°. The reaction mixture was evaporated to dryness *in vacuo*, and the residue extracted with warm ethanol. Sodium thiosulphate (1·7 g.) was left as residue. The extract was evaporated *in vacuo*, and the residue dissolved in ether containing a little ethanol. Slow evaporation of this solution afforded *bis-2-dioctylaminoethyl thiosulphate* (3·2 g.) as waxy plates, m. p. 138° (Found : C, 66·9; H, 11·75; N, 4·3; S, 10·2; Na, 0·1. $C_{36}H_{76}O_2N_2S_2$ requires C, 66·6; H, 11·7; N, 4·3; S, 9·9%) (activity = 5). The *monopicrate* separated from ether as a granular, yellow precipitate (Found : N, 8·2. $C_{42}H_{79}O_{16}N_5S_2$ requires N, 8·0%).

Alkyl 2-Diethylaminoethyl Sulphides.—2-Diethylaminoethyl chloride (48 g., 1·2 mols.) was added to a solution of sodium methyl sulphide (1 mol.), prepared by passing methanethiol into a cooled solution of sodium (7 g.) in absolute ethanol (200 c.c.) (Windus and Shildneck, *Org. Syn.*, 1943, Coll. Vol. II, p. 345), and the mixture warmed gently. A vigorous reaction set in at *ca.* 50° and sodium chloride was precipitated. The reaction was completed by 1 hour's heating under reflux with mechanical stirring. The reaction mixture was filtered, the filtrate evaporated *in vacuo*, and the residue extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue afforded *2-diethylaminoethyl methyl sulphide* (28 g.) as a colourless oil, b. p. 141—145°/150 mm. (Found : N, 9·5. $C_7H_{17}NS$ requires N, 9·5%) (activity = <1 to 1). The hydrochloride crystallised from ethanol–ether in needles but was too hygroscopic for satisfactory analysis.

In the same way butanethiol (b. p. 97—99°; prepared in 25% yield by hydrolysis of sodium butyl thiosulphate with boiling dilute sulphuric acid) gave *butyl 2-diethylaminoethyl sulphide* (80%), b. p. 82°/2·5 mm. (Found : N, 7·4. $C_{10}H_{23}NS$ requires N, 7·4%) [activity = 500—1000; (*s*) 100 (500)]. Octanethiol (b. p. 75—78°/8 mm., prepared in 90% yield by the hydrolysis of sodium octyl thiosulphate) gave *2-diethylaminoethyl octyl sulphide* (89%), b. p. 116—118°/0·7 mm. (Found : N, 5·9. $C_{14}H_{31}NS$ requires N, 5·7%) [activity = >500; (*s*) 50] (Reineckate, m. p. 101—102°), and hexadecanethiol (b. p. 120°/0·7 mm., prepared in 71% yield by hydrolysis of sodium hexadecyl thiosulphate) gave *2-diethylaminoethyl hexadecyl sulphide* (83%), b. p. 184°/0·2 mm. (Found : N, 4·05. $C_{22}H_{47}NS$ requires N, 3·95%) [activity = 100 (500); (*s*) 10] (Reineckate, m. p. 122°).

Butyl 2-diethylaminoethyl sulphide was also prepared in 95% yield from 2-diethylaminoethanethiol (Albertson and Clinton, *J. Amer. Chem. Soc.*, 1945, **67**, 1222) and butyl bromide.

3-Diethylaminopropyl Propyl Sulphide.—Propanethiol (24·5 g.) (Ellis and Reid, *J. Amer. Chem. Soc.*, 1932, **54**, 1684) and trimethylene chlorohydrin (30·7 g.) were added to a solution of sodium (7·5 g.) in absolute ethanol (200 c.c.), and the solution heated under reflux for 1½ hours. The ethanol was removed *in vacuo*, and the product isolated with ether. Distillation gave 3-hydroxypropyl propyl sulphide as a colourless oil (35·0 g.), b. p. 115°/16 mm.

A mixture of this compound (10·0 g.), pyridine (6·0 g., 1 mol.), and chloroform (8 c.c.) was added slowly to thionyl chloride (8·9 g., 1 mol.) in chloroform (8 c.c.) at 10—13°. After 30 minutes the mixture had separated into two layers but became homogeneous on addition of further chloroform (10 c.c.). Next morning, the solution was heated under reflux for 1½ hours, the chloroform was removed *in vacuo*, and the residue was extracted with ether. Distillation of the extract afforded 3-chloropropyl propyl sulphide as a colourless oil (9·0 g.), b. p. 104°/34 mm. This was heated in a sealed tube with diethylamine (16·0 g., 4 mols.) at 120—130° for 5 hours. Diethylammonium chloride was removed, and the filtrate evaporated *in vacuo*. The residual oil was dissolved in light petroleum, and the solution extracted with dilute hydrochloric acid. The acid extracts were basified and the oil was isolated with ether. Distillation gave *3-diethylaminopropyl propyl sulphide* as a colourless oil (4·1 g.), b. p. 138—139°/38 mm. (Found : N, 7·5. $C_{10}H_{23}NS$ requires N, 7·4%) [activity = 10—50; (*s*) 5—10].

Butaldehyde Bis-2-diethylaminoethyl Mercaptal.—2-Diethylaminoethanethiol hydrochloride (12·6 g., 2 mols.) was dissolved in warm chloroform (15 c.c.) and butaldehyde (2·7 g., 1 mol.) was added. The solution was saturated at 10—15° with dry hydrogen chloride, kept overnight, and then warmed to 50° for 1 hour. The chloroform was removed *in vacuo*, and the residue taken up in water and basified with sodium hydroxide. The resultant oil was isolated with ether. Distillation gave the *mercaptal* as a yellow oil (7 g.), b. p. 151—152°/0·7 mm. (Found : N, 8·3. $C_{16}H_{36}N_2S_2$ requires N, 8·7%). The *dihydrochloride* crystallised from ethanol–ether in needles, m. p. 188—189° (Found : N, 7·05. $C_{16}H_{38}N_4Cl_2S_2$ requires N, 7·1%) [activity = 10; (*s*) 5]. The *monohydrochloride*, prepared with one

equivalent of hydrogen chloride, also crystallised from ethanol–ether in needles, m. p. 209—210° (Found : N, 8·3. $C_{18}H_{37}N_2ClS_2$ requires N, 7·9%).

The same product was obtained, but in poorer yield, by condensation of 1 : 1-dichlorobutane with sodium 2-diethylaminoethyl sulphide in methanol.

2-Diethylaminoethyl Octyl Sulphoxide.—The corresponding sulphide (15·0 g.) was dissolved in N-hydrochloric acid (61 c.c., 1 equiv.), 18% (w/v) hydrogen peroxide (13 c.c., 1·33 mols.) was added at such a rate that the temperature did not rise above 28° during the addition, and the mixture was kept overnight. Water and excess of hydrogen peroxide were removed under reduced pressure and the free base was liberated with dilute aqueous ammonia. The *sulphoxide*, isolated with ether, distilled at 138—140°/0·1 mm. as a colourless oil (11 g.) which darkened when kept (Found : C, 63·4; H, 11·6; N, 4·95. $C_{14}H_{31}ONS$ requires C, 64·4; H, 11·9; N, 5·4%) [activity = 10 (100); (*s*) 10 (50)]. The analysis suggests that the compound was contaminated with sulphone. Its Reineckate, crystallised from ethyl acetate–ether, had m. p. 106—107°. This depressed the m. p. of the Reineckate of the original sulphide to 94°.

Alkyl 2-Diethylaminoethyl Sulphones.—Butyl 2-diethylaminoethyl sulphide (7·0 g.) was dissolved in 50% aqueous acetic acid (5 c.c.), and a 3% solution of potassium permanganate in 50% aqueous acetic acid (160 c.c., 5% excess) added with stirring at 0—3°. Oxidation was rapid. The solution was finally decolorised with a little sulphur dioxide and concentrated *in vacuo*, and the residue made alkaline with aqueous ammonia. The resulting oil was isolated with ether and distilled, affording *butyl 2-diethylaminoethyl sulphone* (3·2 g.) as a colourless oil, b. p. 144°/3 mm. (Found : N, 6·3. $C_{10}H_{23}O_2NS$ requires N, 6·3%) [activity = 10; (*s*) 10].

In a similar manner the corresponding *octyl sulphone*, b. p. 152°/0·1 mm. (Found : C, 60·9; H, 10·9; N, 5·0. $C_{14}H_{31}O_2NS$ requires C, 60·65; H, 11·2; N, 5·05%) [activity = 10; (*s*) 5 (10)], was obtained in 80% yield. It gave a Reineckate, m. p. 122°, depressed by the Reineckate of both the sulphide and the sulphoxide. The corresponding *hexadecyl sulphone*, b. p. 205—206·5°/0·07 mm. (Found : N, 3·5. $C_{22}H_{47}O_2NS$ requires N, 3·6%) (activity = 5), was obtained in 58% yield. It gave a Reineckate, m. p. 132°, depressed to 117° by the Reineckate of the sulphide.

Methylbis-2-octylsulphonylethylamine.—Octanethiol (5·84 g., 2 mols.) was added to a solution of sodium (0·92 g., 2 atoms) in absolute ethanol (50 c.c.). At the same time bis-2-chloroethylmethylammonium chloride (3·85 g., 1 mol.) was added to a solution of sodium (0·46 g., 1 atom) in absolute ethanol (50 c.c.), and the two solutions were mixed and heated under reflux for 2 hours. The product, methyldi-(2-octylthioethyl)amine, was isolated as described for the analogous alkyl 2-diethylaminoethyl sulphides and obtained as a colourless oil (5·5 g.), b. p. 175—190°/0·5 mm. Refractionation gave 3·9 g., b. p. 180—186°/0·5 mm. The product was still impure (Found : N, 4·6. Calc. for $C_{31}H_{65}NS_2$: N, 3·7%) but was oxidised directly as described for the corresponding alkyl 2-diethylaminoethyl sulphones. Crystallisation of the product from water gave *methyldi-(2-octylsulphonylethyl)amine* (1·9 g.) as long needles, m. p. 185° after shrinking at 140° (Found : N, 3·0. $C_{31}H_{65}O_4NS_2$ requires N, 3·15%) [activity = 50; (*s*) 10]. The *hydrochloride* separated from ethanol in needles, m. p. 197° after shrinking at 140° (Found : N, 3·0; Cl, 7·1. $C_{31}H_{66}O_4NClS_2$ requires N, 2·9; Cl, 7·4%).

Butyl 2-Diethylaminoethyl Ether.—Sodium (6·9 g.) was dissolved in butanol (300 c.c.), and 2-diethylaminoethyl chloride (40 g.) added. The mixture was heated on the steam-bath, sodium chloride rapidly separating. After 15 hours the mixture was cooled, acidified to Congo-red with concentrated hydrochloric acid, filtered, and evaporated under reduced pressure. The residue was dissolved in water, basified with sodium hydroxide, and isolated with ether. The crude product (38 g.) distilled at 144—148°/200—210 mm. Redistillation failed to afford an analytically pure specimen. It was therefore converted into the *Reinechate*, m. p. 122° (decomp.) after repeated recrystallisation from aqueous methanol (Found : N, 19·6. $C_{14}H_{30}ON_7S_4Cr$ requires N, 19·9%). The free *base* recovered from the Reineckate had b. p. 144°/200 mm. (Found : N, 8·0. $C_{10}H_{23}ON$ requires N, 8·1%) [activity = 1—5; (*s*) 5].

2-Diethylaminoethyl Octyl Ether.—A solution of sodium (2·3 g.) in octanol (175 c.c.) was heated for 20 hours at 100° with 2-diethylaminoethyl chloride (13 g.). The mixture was cooled, diluted with light petroleum (100 c.c.), and extracted with excess of dilute hydrochloric acid. No product was precipitated on basification of the acid extract. The solvent layer was accordingly evaporated *in vacuo*, and the residual solid hydrochloride shaken with ether and dilute sodium hydroxide. Distillation of the ether afforded the pure *ether* (10·9 g.), b. p. 130—133°/10 mm. after redistillation (Found : N, 6·1. $C_{14}H_{31}ON$ requires N, 6·1%) [activity = 50—100; (*s*) 10].

Diethylheptylamine.—A mixture of heptyl bromide (6 g.) and diethylamine (12 g., 5 mols.) was heated in a sealed tube for 4 hours at 130°. The contents of the tube were diluted with ether, and diethylammonium bromide (5·0 g., 98%) filtered off. Distillation of the ethereal extract gave a crude product (4·8 g.), b. p. 154—156°/200 mm., of low nitrogen content (Found : N, 6·6. Calc. for $C_{11}H_{25}N$: N, 8·2%). The crude material was distributed between light petroleum and N-hydrochloric acid. The basic material, re-isolated from the acid extract, gave the pure amine, b. p. 156°/200 mm. (Found : N, 8·4%) [activity = 50; (*s*) 10—50]. Mannich and Davidson (*Ber.*, 1936, **69**, 2106) record b. p. 198°/760 mm. for this compound.

Diethylundecylamine.—A mixture of undecyl bromide (10 g.), diethylamine (7 g., 2·25 mols.), and xylene (10 c.c.) was heated in a sealed tube for 5 hours at 170°. *Diethylundecylamine*, isolated and purified as above, was obtained as a colourless liquid (7·5 g.), b. p. 85—88°/2 mm. (Found : N, 6·4. $C_{15}H_{33}N$ requires N, 6·2%) (activity = 5—10). The only solid derivative obtained was a Reineckate, m. p. 71°.

2-Diethylaminoethyl Nonyl Ketone.—This was prepared by Fry's method (*J. Org. Chem.*, 1945, **10**, 259). A mixture of methyl nonyl ketone (8·5 g., 1 mol.), paraformaldehyde (3·0 g., 2 mols.), diethyl-

ammonium chloride (5·5 g., 1 mol.), concentrated hydrochloric acid (0·2 c.c.), benzene (20 c.c.), and nitrobenzene (20 c.c.) was heated under reflux with stirring. A clear solution was obtained after 15 minutes. After 45 minutes the bath-temperature was raised from 110° to 145°, a water-trap was introduced into the condensing system, and heating was continued for 15 minutes. After cooling, the solution was filtered from a small quantity of crystalline diethylammonium chloride and evaporated *in vacuo*. The residual brown oil only partly solidified. It was accordingly made alkaline, and the free base isolated with ether. Distillation afforded *2-diethylaminoethyl nonyl ketone* as a colourless oil (6·9 g.), b. p. 118—122°/0·5 mm. (Found: N, 5·7. $C_{16}H_{33}ON$ requires N, 5·5%) (activity = 1—5).

Bis-2-diethylaminoethyl Sulphoxide.—Bis-2-diethylaminoethyl sulphide (4·6 g.; b. p. 106—110°/2 mm.) (Gilman, Plunkett, Tolman, Fullhart, and Broadbent, *J. Amer. Chem. Soc.*, 1945, **67**, 1846) was suspended in ice-cold water (15 c.c.), and bromine water added with stirring in slight excess as shown by a faint yellow colour. The solution was evaporated *in vacuo*, and the residue dissolved in boiling ethanol (300 c.c.). On cooling, the *sulphoxide dihydrobromide* separated as colourless small needles (5·5 g.), m. p. 224° (decomp.) (Found: N, 6·8. $C_{12}H_{30}ON_2Br_2S$ requires N, 6·8%) (activity = <1). Titration with acid potassium permanganate resulted in the uptake of almost exactly two atoms of oxygen, corresponding to oxidation of the sulphoxide to sulphone and of the hydrogen bromide to bromine.

Bis-2-diethylaminoethyl Sulphone.—A solution of potassium permanganate (3 g., 10% excess) in 50% acetic acid (200 c.c.) was added with stirring at 0° to a solution of bis-2-diethylaminoethyl sulphide (10 g.) in 50% acetic acid (10 c.c.) during 45 minutes. After a further 20 minutes, the brown solution was decolorised with sulphur dioxide and evaporated to dryness *in vacuo*. The residue was dissolved in hot absolute ethanol and treated with excess of ethanolic ammonia. The inorganic salts were removed and re-extracted with absolute ethanol, and the united filtrates evaporated to dryness. The residual gum was extracted with warm absolute ethanol and filtered. Addition of ethanolic hydrogen chloride to the filtrate gave the *sulphone dihydrochloride* as colourless needles (6·0 g.), m. p. 202° after recrystallisation from ethanol (Found: N, 8·3. $C_{12}H_{30}O_2N_2Cl_2S$ requires N, 8·3%) (activity = <1).

Bis-2-diethylaminoethyl Disulphide.—2-Diethylaminoethanethiol hydrochloride, needles, m. p. 172—173°, from ethanol–ether, was exposed to air overnight. Crystallisation of the resulting solid from ethanol–ether gave the disulphide dihydrochloride as needles, m. p. 220° (Found: N, 8·5. Calc. for $C_{12}H_{30}N_2Cl_2S_2$: N, 8·3%) [activity = 10; (*s*) 5]. Gilman *et al.* (*loc. cit.*) record m. p. 216—217°.

p-*Aminophenyl 2-Diethylaminoethyl Sulphone.*—2-Diethylaminoethyl chloride (27·0 g., 1·1 mols.) was added to a solution of sodium *p*-acetamidobenzenesulphinate (1 mol.), prepared by adding *p*-acetamidobenzenesulphinic acid (35 g.; Smiles and Bere, *Org. Synth.*, 1941, Coll. Vol. I, p. 7) to a solution of sodium (4·0 g.) in absolute ethanol (500 c.c.), and the mixture was heated under reflux. Sodium chloride began to separate after about 5 minutes. After 1½ hours the reaction mixture was cooled, filtered from sodium chloride, and concentrated *in vacuo* to about half its volume. At this point a *substance* (3 g.) of unknown composition separated as fine needles, m. p. 284° (Found: N, 7·2%). The filtrate from this solid was further evaporated to dryness and the residual gum treated with 2N-hydrochloric acid (100 c.c.). The insoluble residue consisted of a mixture of *p*-acetamidobenzenesulphinic acid (3·5 g.) and the above compound, m. p. 284° (1·5 g.). The acid-soluble p-*acetamidophenyl 2-diethylaminoethyl sulphone* was precipitated by sodium hydroxide as a colourless solid, crystallising from benzene in needles (16 g.), m. p. 93—94° (Found: N, 8·9. $C_{14}H_{22}O_3N_2S$ requires N, 9·4%).

The above compound (7 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (180 c.c.). The cooled solution was made alkaline to litmus with sodium hydroxide. The oily precipitate solidified on cooling to 0° and was collected and redissolved in boiling water (250 c.c.). On cooling, p-*aminophenyl 2-diethylaminoethyl sulphone* (4·7 g.) separated in long needles, m. p. 55° (Found: N, 10·8. $C_{12}H_{20}O_2N_2S$ requires N, 10·9%) (activity = <1).

*Toluene-*p*-sulphonylmethylamines.*—A solution of hydroxymethyl *p*-tolyl sulphone (2·0 g.) (Meyer, *loc. cit.*) and methylaniline (1·14 g., 1 mol.) in ether (75 c.c.) quickly deposited N-(*toluene-*p*-sulphonylmethyl)aniline* (2·05 g.), needles, m. p. 109° (Found: N, 5·5. $C_{15}H_{17}O_2NS$ requires N, 5·4%). The following compounds were prepared similarly, the solvent for the condensation being given in parentheses: N^4-(*toluene-*p*-sulphonylmethyl)sulphanilamide* (from methanol), flat needles, m. p. 166—167° (Found: N, 8·6. $C_{14}H_{16}O_4N_2S_2$ requires N, 8·25%) (activity = <1); *2-methyl-5-(toluene-*p*-sulphonylmethylamino)-1 : 3 : 4-oxadiazole*, fine needles (from chloroform), m. p. 170° (Found: N, 15·8. $C_{11}H_{13}O_3N_3S$ requires N, 15·7%) (activity = <1); *4-(toluene-*p*-sulphonylmethyl)morpholine*, plates (from ether), m. p. 86—88° (Found: N, 5·5. $C_{12}H_{17}O_3NS$ requires N, 5·5%).

The authors gratefully acknowledge their indebtedness to Dr. L. Dickinson and Miss B. Croshaw for the biological tests, and to Dr. W. F. Short for his interest in the work described in this and the preceding paper. They also thank Mrs. Ward and Mrs. K. Weston for carrying out the analyses.

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[*Received, May 29th*, 1951.]

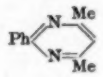
728. *The Ultra-violet Absorption Spectra of Phenylpyrimidines.*

By Allison Maggiolo and Peter B. Russell.

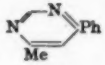
The attachment of a phenyl nucleus to a pyrimidine nucleus in any of the available positions causes shift to longer wave-length and an increase in intensity of the absorption maximum. This exaltation is diminished by the interference with the planarity of the molecule by substitution about the joining bond. The spectroscopic phenomena are analogous in some respects to those previously observed in the diphenyl series and, like them, they may be readily accounted for on the quasi-classical theory of Lewis and Calvin (*Chem. Reviews*, 1939, **25**, 273). From a study of these phenomena and their interpretation, certain conclusions are drawn as to the nature of the pyrimidine ring.

In a recent communication (Russell and Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3763) mention was made of some rather marked differences in the ultra-violet absorption spectra of 2 : 4-diaminopyrimidines with phenyl groups in the 5- and the 6-position. Since the former group of compounds show high antimalarial activity while the latter are inactive, an attempt has been made to gain an insight into the differences in fine structure of these compounds from a study of these spectra. The present paper deals with the spectra of the parent 2-, 4-, and 5-phenylpyrimidines. For purely practical reasons it has in some cases been necessary to utilize the spectra of methyl derivatives of these compounds. There is, however, every reason to believe that the introduction of this substituent, except possibly when placed adjacent to the ring junction, has little or no effect on the resulting spectrum.

4 : 6-Dimethyl-2-phenyl- (I) (Pinner, *Ber.*, 1893, **26**, 2124), 6-methyl-4-phenyl- (II) (von Merkatz, *Ber.*, 1919, **52**, 869), and 5-phenyl-pyrimidine (III) were examined. Their spectra



(I)



(II)

(III)

are shown in Fig. 1 and listed in the table together with the spectra of diphenyl and the three phenylpyridines.

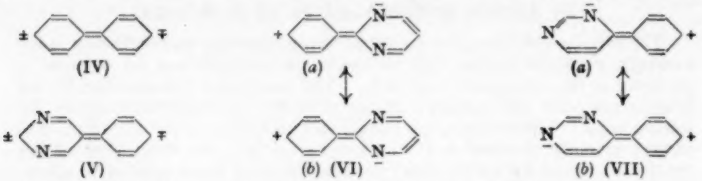
Compound	$\lambda_{max.}$, mμ	$\varepsilon_{max.}$	Compound	$\lambda_{max.}$, mμ	$\varepsilon_{max.}$
(I)	258	20,200	3-Phenylpyridine [2]	246	17,200
(II)	273	18,000		275 infl.	10,000
(III)	256	12,100	4-Phenylpyridine [2]	257	16,000
Pyrimidine [1]	242	2,500	Pyridine [3]	253	1,820
2-Phenylpyridine [2]	245	12,700	Diphenyl [4]	246	20,300
	276	11,300	Benzene [5]	197	4,360
				255	213

[1] Uber and Winters, *J. Amer. Chem. Soc.*, 1941, **63**, 137. [2] Gillam, Hey, and Lambert, *J.*, 1941, 364. [3] International Critical Tables, Vol. V, 363. [4] Gillam and Hey, *J.*, 1939, 1170. [5] Henri, *J. Phys. Radium*, 1922, **3**, 181.

The relation between colour and chemical constitution has recently received renewed attention (Braude, *Ann. Reports*, 1945, **42**, 105; Maccoll, *Quart. Reviews*, 1947, **1**, 144; Bowen, *ibid.*, 1950, **4**, 236; Ferguson, *Chem. Reviews*, 1948, **43**, 385). Although the theoretical status of the subject is not entirely satisfactory, a qualitative interpretation of the spectra of many compounds can be based on the concept of resonance and on the theory of Lewis and Calvin (*loc. cit.*; see also Branch and Calvin, " The Theory of Organic Chemistry," Prentice-Hall Inc., New York, 1943, pp. 155 *et seq.*). These authors ascribe the absorption of light by diphenyl to electronic oscillations, the extremes of which may be represented by (IV). These are resonance forms contributing particularly to the excited state of the molecule.

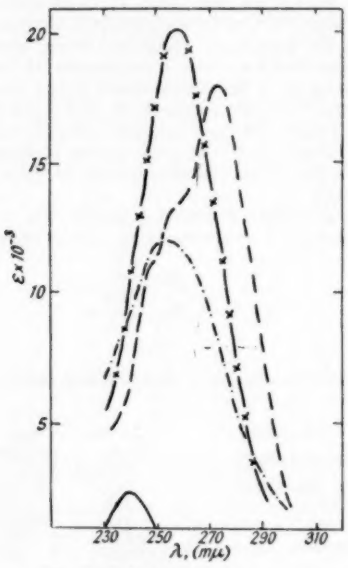
Although similar forms (V) can be written for 5-phenylpyrimidine, yet for both 2- and 4-phenylpyrimidine forms are possible where the negative charge is carried on a ring nitrogen (VI*a* and *b*, and VII*a* and *b*). In these two cases the favourable disposition of charge should lead to increased contribution of the ionoid forms (Branch and Calvin, *op. cit.*, p. 267). The effect of this is observed in the spectra of (I) and (II), the maxima here being much more intense than that shown by (III). In addition, (II), which can give rise to unsymmetrical ionoid

forms (VII*a* and *b*), shows a complicated spectrum with inflexions at 250 and 260 mμ. In the phenylpyridine series (Hey, Gillam, and Lambert, *loc. cit.*, see table) complexity of spectra is



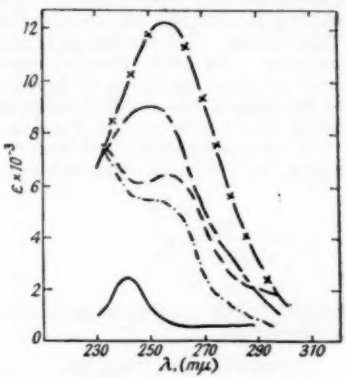
also associated with lack of symmetry, for both 2- and 3-phenylpyridine, (VIII) and (IX), show complex spectra while 4-phenylpyridine (X) shows a single sharp peak.

FIG. 1.



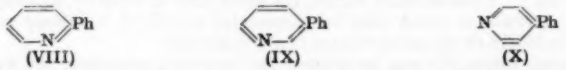
——————— *Pyrimidine.*
—×—×— 4 : 6-*Dimethyl-2-phenylpyrimidine* (I).
— — — — 6-*Methyl-4-phenylpyrimidine* (II).
— · — · — 5-*Phenylpyrimidine* (III).
[*All in ethyl alcohol* (10 *mg./l.*).]

FIG. 2.



——————— *Pyrimidine.*
—×—×— 5-*Phenylpyrimidine* (III).
— — — — 4-*Chloro-5-phenylpyrimidine* (XI).
— — — — 4 : 6-*Dichloro-2-methyl-5-phenylpyrimidine* (XII).
— · — · — 4-*Chloro-5-o-chlorophenylpyrimidine* (XIII).
[*All in ethyl alcohol* (10 *mg./l.*).]

It is to be remarked that the introduction of a phenyl nucleus into the 5-position of the pyrimidine nucleus causes a shift and increase in intensity of the absorption which is smaller than the shift and intensity change caused by the joining of two phenyl nuclei [compare pyrimidine and 5-phenylpyrimidine with benzene (intense band at about 200 mμ) and diphenyl in the



table]. This effect must again be ascribed to the fact that the C–N bond is more polar than the C–C bond, the nitrogen tending to remove some of the negative charge from the neighbouring carbon atom with a consequent reduction of the ionoid form of (V) which carries the negative charge on $C_{(2)}$ of the pyrimidine nucleus.

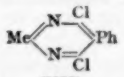
The hypothesis that the increase in wave-length and intensity of the band in the spectrum

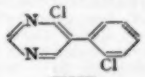
of 5-phenylpyrimidine (III) over the values for pyrimidine itself is due to contributions to the excited state of the molecule of the forms (V) may be tested directly. The concept of a non-planar coaxial structure for diphenyls substituted in the positions *ortho* to the ring junction is generally accepted (Shriner, Adams, and Marvel, in Gilman's "Organic Chemistry," Wiley and Sons, New York, 2nd edn., Vol. I, p. 352; Muller, *Fort. Chem. Forschung*, 1949, **1**, 325). Theoretically, it is to be expected that departure from a coplanar configuration of rings should reduce and ultimately prevent contributions from the ionoid structures (IV) to the excited state of the diphenyl molecule. Corresponding changes would be expected in the absorption spectrum, and these have been observed (Pickett *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 2296; 1950, **72**, 44; Rodebush *et al.*, *ibid.*, 1940, **62**, 2906; 1941, **63**, 3018; Sherwood and Calvin, *ibid.*, 1941, **63**, 1350; Jones, *ibid.*, p. 1658).

Although diphenyl itself is planar in the solid state (Dhar, *Indian J. Physics*, 1932, **7**, 43), yet in the gaseous state the rings are inclined to one another (Karle and Brockway, *J. Amer. Chem. Soc.*, 1944, **66**, 1977). This departure from co-planarity is not great enough to inhibit the conjugation between the rings to any considerable extent; however, its effect on the absorption spectrum of diphenyl both as a gas and in solution has been observed (Merkel and Wieband, *Z. Naturforsch.*, 1948, **3** *b*, 93). For the purposes of the present discussion, however, molecules which, like that of diphenyl, have no atoms other than hydrogen in the position *ortho* to the ring junction are referred to as planar.

It would appear, therefore, that if the spectroscopic effects of a phenyl group in the 5-position of the pyrimidine ring are, in fact, due to contributions from ionoid forms such as (V), then the 5-phenylpyrimidine molecule must be essentially planar and destruction of this planarity should cause marked changes in the absorption spectrum. A series of 5-phenylpyrimidines in which the positions adjacent to the ring junction carry chlorine atoms was prepared, *viz.*, 4-chloro-5-phenyl- (XI) (Davies and Piggott, *J.*, 1945, 347), 4 : 6-dichloro-2-methyl-5-phenyl- (XII), and 4-chloro-5-*o*-chlorophenyl-pyrimidine (XIII). The absorption maxima of these compounds showed a marked decrease in intensity compared with that of the parent 5-phenylpyrimidine

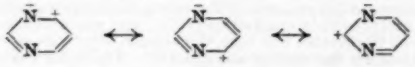
(XI)


(XII)


(XIII)

(see Fig. 2). The change was least with (XI) and greatest with (XIII), (XII) being intermediate. The spectrum of (XIII) approximates to an addition curve of the two ring systems involved, indicating virtual absence of contribution from ionoid forms such as (V). It should be noticed that the effects observed here are of a higher order than, and in the opposite direction to, those resulting from the introduction of chlorine atoms into pyrimidine itself (Uber and Winters, *loc. cit.*).

The reported observations show a great similarity in behaviour between a benzene and a pyrimidine ring. The most probable explanation is the conclusion that pyrimidine possesses a highly "aromatic" character, resembling benzene in size, shape, and other properties. However, the lower degree of conjugation in a 5-phenylpyrimidine as compared with diphenyl and the large contributions of forms such as (VI) and (VII) to 2- and 4-phenylpyrimidine suggest that the ionoid forms (XIV and three equivalent forms with the negative charge on the other nitrogen atom) are more important in pyrimidine than are the corresponding Dewar forms in benzene. The importance of the Kekulé forms (XV) is correspondingly reduced.


(XIV)

(XV)

These conclusions are at variance with those of other workers (Cavalieri and Bendich, *J. Amer. Chem. Soc.*, 1950, **72**, 2587) who, from a study of the spectra of hydroxy- and amino-pyrimidines, concluded that the pyrimidine ring has a "low degree of aromaticity." However, the views expressed herein are in agreement with those reached from a study of the chemistry of pyrimidines (Lythgoe, *Quart. Review*, 1949, **3**, 194), from the results of *X*-ray studies on pyrimidines (Clews and Cochran, *Acta Cryst.*, 1949, **2**, 46), and from estimates of the resonance energy of pyrimidines which is some 30 kcals./mole (Maccoll, *J.*, 1946, 670; Dewar, "Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 36).

The removal of chlorine from 4-chloro-5-phenylpyrimidine by catalytic or chemical reduction

has been reported not to give the required 5-phenylpyrimidine (III) (Davies and Piggott, *loc. cit.*). This finding was confirmed. However, (III) was formed readily when the corresponding 4-mercapto-5-phenylpyrimidine, prepared by alkaline hydrolysis of the corresponding thiuronium salt (Polonovski and Schmitt, *Bull. Soc. chim.*, 1950, 616), was heated with Raney nickel in alcohol. This procedure for removal of sulphur was also found to be useful in the preparation of 4-methyl-6-phenylpyrimidine (II) from the corresponding 2-mercaptopyrimidine. Previously (II) had been prepared by the route 2-mercapto- ⟶ 2-hydroxy- ⟶ 2-chloropyrimidine ⟶ (II) (von Merkatz, *loc. cit.*).

Experimental.

4-Methyl-6-phenylpyrimidine.—2-Mercapto-4-methyl-6-phenylpyrimidine (4 g.) (von Merkatz, *loc. cit.*) was dissolved in ethanol (100 c.c.). Raney nickel (13 g.) was added, and the solution refluxed for 3 hours. The nickel was then filtered off, and the solvent removed under reduced pressure. The oily residue was dissolved in ether from which it crystallized on addition of light petroleum (b. p. 30—60°) and cooling. It formed almost colourless crystals, m. p. 42—43° (von Merkatz, *loc. cit.*, gives 44—45°) (Found: N, 16·3. Calc. for $C_{11}H_{10}N_2$: N, 16·5%).

4 : 6-Dihydroxy-2-methyl-5-phenylpyrimidine.—Ethyl phenylmalonate (11·3 g.) (Rising and Stieglitz, *J. Amer. Chem. Soc.*, 1918, **40**, 727) was added to a solution of acetamidine prepared from the hydrochloride (4·2 g.) and a solution of sodium (1·15 g.) in ethanol (50 c.c.). The solution was refluxed on a steam-bath for 20 hours, then poured into water (200 c.c.), and made acid with acetic acid. The *pyrimidine* separated and was filtered off. After recrystallization from boiling water, it formed colourless plates which did not melt below 350° (Found: C, 65·2; H, 5·0; N, 14·2. $C_{11}H_{10}O_2N_2$ requires C, 65·4; H, 5·0; N, 13·9%).

4 : 6-Dichloro-2-methyl-5-phenylpyrimidine (XII).—The above dihydroxypyrimidine (3·5 g.) was heated with phosphoryl chloride (20 c.c.) under reflux for 40 minutes. After removal of the excess of phosphoryl chloride, the residual oil was poured on cracked ice (200 g.), and the mixture made alkaline with ammonia. The *dichloropyrimidine* (3·2 g.) was filtered off and recrystallized from benzene. It formed white prisms, m. p. 162—163° (Found: N, 11·9. $C_{11}H_{10}N_2Cl_2$ requires N, 11·7%).

5-Phenylpyrimidine.—4-Chloro-5-phenylpyrimidine (XI) (Davies and Piggott, *loc. cit.*) (10 g.) and thiourea (4·5 g.) were dissolved in alcohol (20 c.c.), and the solution refluxed for 5 hours. After cooling, the crystalline thiuronium compound (cf. Polonovski and Schmitt, *loc. cit.*) (6 g.) was collected and refluxed with 2N-sodium hydroxide solution for 1 hour, the solution was acidified, and the gummy thiol heated with Raney nickel (8 g.) in alcohol (50 c.c.). After 3 hours, the nickel was filtered off, and the alcohol evaporated under reduced pressure. The *5-phenylpyrimidine* formed an oil which solidified and remelted at about 25°. It boiled at 120—140° (bath-temp.)/0·01 mm., to give a clear yellow oil which crystallized at about 23—27° (Found: N, 17·8. $C_{10}H_8N_2$ requires N, 17·9%).

The base (0·5 g.) was converted into the nitrate by dissolving it in 25% aqueous nitric acid (1·0 c.c.) and adding a saturated solution of potassium nitrate (0·5 c.c.). On cooling, the *nitrate hemihydrate* separated as colourless prisms, m. p. 181—183° (Found: C, 52·3; H, 4·4. $C_{10}H_8N_2,HNO_3,\frac{1}{2}H_2O$ requires C, 52·6; H, 4·4%).

4-Amino-5-o-chlorophenylpyrimidine (cf. Davies, Johnson, and Piggott, *J.*, 1945, 352).—Formamide (50 g.) and *o*-chlorophenylacetonitrile (30 g.) were heated at 180° for 14 hours under reflux. The cooled mixture was poured into water (500 c.c.), acidified with 3N-hydrochloric acid (200 c.c.), and the whole was warmed on a steam-bath and stirred for 1 hour; the insoluble oil was separated with ether, and the aqueous solution was basified with 3N-sodium hydroxide and cooled; the resulting *base* (20 g.) was collected and crystallized from benzene, forming colourless crystals, m. p. 180° (Found: C, 58·3; H, 3·7; N, 20·2. $C_{10}H_8N_3Cl$ requires, C, 58·5; H, 3·9; N, 20·4%).

5-o-Chlorophenyl-4-hydroxypyrimidine.—The above aminopyrimidine (8 g.) was heated under reflux with concentrated hydrochloric acid (30 c.c.) for 16 hours. The whole reaction mixture was then brought to pH 11 with 6N-sodium hydroxide, treated with charcoal, and filtered. On acidification with acetic acid the *pyrimidine* separated as colourless crystals (7·5 g.), which recrystallized from benzene–alcohol in needles, m. p. 136—137° (Found: N, 13·4. $C_{10}H_7ON_2Cl$ requires N, 13·5%).

4-Chloro-5-o-chlorophenylpyrimidine (XIII).—The above hydroxy-pyrimidine (7 g.) was heated with phosphoryl chloride (30 c.c.) under reflux for ½ hour. After removal of the excess of phosphoryl chloride, the residue was dissolved in chloroform (50 c.c.) and poured on cracked ice (200 g.) and made alkaline with ammonia. The mixture was stirred violently for 10 minutes and then the organic layer was separated and dried (Na_2SO_4). After removal of the chloroform the residue was distilled. The colourless *chloropyrimidine* boiled at 150—160° (bath-temp.)/0·01 mm. (5·5 g.). It solidified to a colourless crystalline mass, m. p. 20—21° (Found: C, 53·1; H, 2·5; N, 12·1. $C_{10}H_6N_2Cl_2$ requires C, 53·4; H, 2·7; N, 12·4%).

Absorption Spectra.—These were determined by using a Beckman model D.U. quartz spectrophotometer (cell length, 1 cm.). The solutions were made in purified alcohol at a concentration of 10 mg./l.

The authors thank Mr. S. Blackman and Mr. N. Martinez, Jr., for the microanalyses and Miss Pheobe Lee Graham for the spectroscopic determinations. Thanks are also due to Drs. George H. Hitchings and R. Baltzly, of these Laboratories, and to Dr. George Kenner, of the University Chemical Laboratory, Cambridge, for their friendly interest and enlightening discussions.

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[*Received, July 9th*, 1951.]

729. *Nucleophilic Displacement of Fluorine from Organic Compounds. Part I. Kinetics of the Reactions of 1-Fluoro-2 : 4-dinitrobenzene with Primary Aromatic Amines.*

By N. B. Chapman and R. E. Parker.

The Arrhenius parameters for the reactions of 1-fluoro-2 : 4-dinitrobenzene with primary aromatic amines in 99·8% ethanol have been determined. The energy of activation is ~5000 cals. less than for the corresponding reactions of chloro- and bromo-compounds, and $\log_{10} A$ is 1·3—3·0 units less. This is ascribed mainly to an accentuated increase in solvation of the transition state in the reactions of the fluoro-compound. The fluoro-compound consumes only one mole of amine per mole and reacts ~100—200 times as fast as the chloro-compound at 30°, and ~20—70 times as fast at 50°. The mechanism of the reaction and values of the Arrhenius parameters are discussed, with special reference to a theory advanced by Berliner, Quinn, and Edgerton (*J. Amer. Chem. Soc.*, 1950, **72**, 5305) for analogous reactions of halogenonitronaphthalenes.

The kinetics of nucleophilic displacement of fluorine from organic compounds have not been much investigated, possibly because many organic fluorides apparently react very slowly with nucleophilic reagents. However, the kinetics of the reactions of 2-fluoroethanol with hydroxide ions have been examined (McCabe and Warner, *J. Amer. Chem. Soc.*, 1948, **70**, 4031) and the reactions of *n*-amyl, *cyclo*hexyl, and *tert.*-amyl fluorides, among others, with ethoxide ions have been recently studied in these laboratories (unpublished work by J. L. Levy). Aromatic fluoro-compounds of suitable structure react smoothly and relatively rapidly even with weakly nucleophilic reagents such as aromatic amines: 1-fluoro-2 : 4-dinitrobenzene is typical of these compounds, and for that reason has been chosen for study. The kinetics of the reactions of halogeno-2 : 4-dinitrobenzenes with amines have been the subject of a fair amount of investigation by Blanksma and Schreinemachers (*Rec. Trav. chim.*, 1933, **52**, 428), Singh and Peacock (*J.*, 1935, 1410; *J. Phys. Chem.*, 1936, **40**, 669), and Brady and Cropper (*J.*, 1950, 507). The present paper records the results of the first investigation of the kinetics of such reactions when the displaced halogen is fluorine, with the object of elucidating the causes of the relatively high rates of reaction.

Primary aromatic amines have been chosen as nucleophilic reagents for three main reasons: (*a*) the corresponding reactions of these amines with 1-chloro-2 : 4-dinitrobenzene have been thoroughly studied by Singh and Peacock (*loc. cit.*) and by van Opstall (*Rec. Trav. chim.*, 1933, **52**, 901); (*b*) the reactions can be studied by bromometric determination of the unchanged amine for a suitable range of amines, whereas the determination of fluoride ion, in contrast to that of other halide ions, is not well adapted to kinetic studies; (*c*) there was reason to believe, by analogy with Singh and Peacock's work (*loc. cit.*), that the reactions of the different amines, appropriately chosen, would have nearly the same entropies of activation, thus simplifying the interpretation of the results.

Additional interest attaches to the behaviour of 1-fluoro-2 : 4-dinitrobenzene since it has found a valuable application in "labelling" free amino-groups in proteins before hydrolysis (Sanger, *Biochem. J.*, 1945, **39**, 507; 1946, **40**, 261; 1948, **42**, 287). 1-Fluoro-2 : 4-dinitrobenzene owes its use in the above way to the remarkable ease with which the fluorine is displaced—this property has also been exploited in a preparative way by Whalley (*J.*, 1950, 2241) to convert alcohols into the corresponding 2 : 4-dinitrophenyl ethers by the action of 1-fluoro-2 : 4-dinitrobenzene in the presence of *tert.*-amines. Rarick, Brewster, and Dains (*J. Amer. Chem. Soc.*, 1933, **55**, 1289) employed *p*-fluoronitrobenzene similarly.

For kinetic studies with nucleophilic reagents Lulofs (*Rec. Trav. chim.*, 1901, **20**, 292) chose alkoxide ions, whereas Singh and Peacock, van Opstall, and Blanksma and Schreinemachers (*locc. cit.*), and Rheinlander (*J.*, 1923, 3099) used either aliphatic or aromatic amines or ammonia. The most relevant of these results for our purposes are those of Singh and Peacock, and of van Opstall, and we shall return to these in the discussion. Le Roux, Lu, Sugden, and Thomson (*J.*, 1945, 586) and Bennett and Vernon (*J.*, 1938, 1783) have studied the simplest of all nucleophilic displacements with these compounds, *viz.*, when the reagent is a halide ion, either isotopically distinguished from, as in the former case, or chemically different from, the

halogen present in the organic compound, as in the latter case. However, no reactions in which fluorine is displaced, nor yet when it is the attacking reagent, have so far been studied.

The Arrhenius parameters for the reactions of 1-fluoro-2 : 4-dinitrobenzene with a series of primary aromatic amines in 99·8% ethanol are now presented. It has been possible to formulate a mechanism for the reactions and to suggest the causes of the observed reaction velocities, relative to those of other analogous halogeno-compounds. A brief preliminary account of this work has already been given (Chapman, Parker, and Soanes, *Chem. and Ind.*, 1951, 148).

Experimental.

(M. p.s are uncorrected.)

Materials.—1-Fluoro-2 : 4-dinitrobenzene, m. p. 26·5—27·0°, was prepared by Cook and Saunders's method (*Biochem. J.*, 1947, **41**, 558). After fractionation at 2 mm. the product was crystallised to constant m. p. from absolute ethanol.

The amines were all purified by crystallisation of their acetyl derivatives, followed by fractionation or crystallisation of the free bases (cf. Singh and Peacock, *loc. cit.*). The m. p.s of the acetyl derivatives and of the solid amines agreed with those given by these authors.

The hydrofluorides of aniline and *m*-bromoaniline were prepared by dropwise addition of 40% (wt.) hydrofluoric acid (6 g.) to a stirred solution of the amine (0·2 mol.) in absolute ethanol (10 c.c.) at 0°. The precipitated hydrofluorides were filtered off, sucked dry, well washed with benzene, and allowed to dry in the air. Thus were obtained aniline hydrofluoride (Found: $C_6H_5{\cdot}NH_2$, 70·5; HF, 15·2. Calc. for C_6H_7N,HF,H_2O: $C_6H_5{\cdot}NH_2$, 71·0; HF, 15·3%) and *m*-bromoaniline hydrofluoride (Found: m-$C_6H_4Br{\cdot}NH_2$, 82·0; HF, 13·5%. These figures were reproducible but do not correspond to any integral formula). Both the products deteriorated on storage and were freshly prepared before use.

The ethanol was purified by drying the commercial absolute product by Lund and Bjerrum's method (*Ber.*, 1931, **64**, 210) and fractionating the product. The water content of the ethanol was determined by the Karl Fischer reagent as modified by Smith, Bryant, and Mitchell (*J. Amer. Chem. Soc.*, 1939, **61**, 2407), and water was added to give 99·80% (by wt.) ethanol.

Thermostats.—A well-stirred mixture of crushed ice and water gave a steady temperature of 0·10°. For the higher temperatures the usual arrangement was employed: temperatures were steady to ±0·05°.

Procedure.—A solution (15 c.c.) of 1-fluoro-2 : 4-dinitrobenzene in 99·80% ethanol of definite concentration, about 0·020M., at thermostat temperature was added to a similar solution (10 c.c.) of amine, about 0·125M., in each of several 25-c.c. stoppered graduated flasks already in the thermostat. At known intervals the contents of a flask were poured into a mixture of benzene (50 c.c.) and concentrated hydrochloric acid (25 c.c.). This stopped the reaction by converting all the free amine into its hydrochloride. The flask was washed twice with distilled water, and the washings were added to the benzene–acid mixture. The benzene layer, containing unchanged fluorodinitrobenzene and most of the substituted diphenylamine produced, was separated and washed twice with water.

The residual amine in the combined aqueous layers was determined bromometrically following Day and Taggart's procedure (*Ind. Eng. Chem.*, 1928, **20**, 545). The excess of bromate–bromide solution never exceeded about 3 c.c. of 0·1N-solution. Under these conditions it was shown that none of the other substances possibly present, particularly ethanol, interferes. With larger excesses of bromate–bromide solution ethanol is oxidised. In all cases the accuracy of the procedure was checked by carrying out a blank. In some cases the initial amine concentration determined in this way differed from that calculated from the weight of amine, by up to 0·5%, and the concentration determined by titration was then used to calculate the rate constants given below.* As a further check the amount of free amine left after "infinite" time was determined. This usually corresponded to between 99·0% and 100% reaction.

Products.—2 : 4-Dinitrodiphenylamine and its various derivatives were isolated and characterised by their m. p.s.

Results.

The reactions with aniline and with *m*-bromoaniline, both at 30°, were each carried out at three different initial concentrations, and by application of the differential method of determining orders (Laidler, "Chemical Kinetics," New York, 1950, p. 14), were shown to be of the first order with respect both to the fluoro-compound and to the amine. This was assumed to hold for the other cases also, as they all obeyed the second-order rate law given below.

By comparing the velocity coefficients assembled in Table I it was concluded that the reactions are represented by the equation

$$Ar{\cdot}NH_2 + Ar'F = Ar{\cdot}NHAr' + HF$$

Under the conditions of our experiments the liberated hydrogen fluoride does not apparently fix the amine and render it incapable of reaction (cf. Singh and Peacock's results with 1-chloro-2 : 4-dinitrobenzene, *loc. cit.*) since the amine hydrofluorides react almost as rapidly as the free amines.

* In a preliminary report of this work (Chapman, Parker, and Soanes, *loc. cit.*) the rate constants were calculated by using initial amine concentrations calculated from the weight of amine. This explains the slight discrepancies.

The rate law is therefore

$$dx/dt = k(a - x)(b - x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

giving

$$k = \frac{2{\cdot}303}{t(a - b)} \log_{10} \frac{b(a - x)}{a(b - x)}$$

where a = initial concentration of amine and b = initial concentration of fluorodinitrobenzene.

TABLE I.

k is in l. mole^{-1} sec.$^{-1}$.

Reagent	Temp.	$k \times 10^4$	Reagent	Temp.	$k \times 10^4$
Aniline	40°	122	*m*-Bromoaniline	30°	2·04
Aniline hydrofluoride	40	114	*m*-Bromoaniline hydrofluoride	30	1·85

TABLE II.

Aniline. 0·0503M-NH_2Ph, 0·0125M-$C_6H_3F(NO_2)_2$; 30°.

Time (secs.)	242	902	1908	3661	8032	17 hrs.
Decompn., %	9·60	31·44	53·84	75·28	93·46	99·36
10^4k	84·0	86·9	87·3	86·1	81·1	

Mean $k = 85{\cdot}1 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

m-*Toluidine.* 0·0497M-$NH_2{\cdot}C_6H_4Me$, 0·0125M-$C_6H_3F(NO_2)_2$; 20°.

Time (secs.)	802	1094	1364	1632	1919	2224
Decompn., %	31·63	40·34	47·12	52·96	58·63	62·94
10^4k	99·6	100·6	100·7	100·6	101·2	99·1

Mean $k = 100{\cdot}3 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

p-*Chloroaniline.* 0·0497M-$NH_2{\cdot}C_6H_4Cl$, 0·0125M-$C_6H_3F(NO_2)_2$; 40°.

Time (secs.)	4333	6615	18,377	30,660	124 hrs.
Decompn., %	28·16	38·88	71·12	86·16	100·6
10^4k	16·0	15·8	15·3	15·2	—

Mean $k = 15{\cdot}6 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

p-*Bromoaniline.* 0·0499M-$NH_2{\cdot}C_6H_4Br$, 0·0125M-$C_6H_3F(NO_2)_2$; 30°.

Time (secs.)	2687	10,115	19,980	40,440	89,700	127 hrs.
Decompn., %	9·59	30·06	48·92	72·58	92·65	99·92
10^4k	7·62	7·39	7·25	7·23	7·00	—

Mean $k = 7{\cdot}30 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

m-*Chloroaniline.* 0·0492M-$NH_2{\cdot}C_6H_4Cl$, 0·0125M-$C_6H_3F(NO_2)_2$; 20°.

Time (mins.)	1225	1345	1496	2667	3142	4035
Decompn., %	37·04	39·92	43·44	61·60	67·76	75·44
10^4k	1·35	1·36	1·38	1·34	1·36	1·34

Mean $k = 1{\cdot}36 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

m-*Bromoaniline.* 0·0495M-$NH_2{\cdot}C_6H_4Br$, 0·0126M-$C_6H_3F(NO_2)_2$; 40°.

Time (mins.)	118·3	385·7	1072	1469	2840	340 hrs.
Decompn., %	10·33	29·55	60·29	71·17	89·28	98·01
10^4k	3·14	3·19	3·19	3·21	3·14	—

Mean $k = 3{\cdot}17 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

Aniline hydrofluoride. 0·0247M-NH_2Ph,HF,H_2O, 0·0125M-$C_6H_3F(NO_2)_2$; 40°.

Time (secs.)	348	1317	2709	5150	11,248	46 hrs.
Decompn., %	8·99	29·70	48·48	68·06	87·64	99·52
10^4k	109	114	115	118	112	—

Mean $k = 114 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

m-*Bromoaniline hydrofluoride.* 0·0257M-$NH_2{\cdot}C_6H_4Br,1{\cdot}4HF,0{\cdot}5H_2O$, 0·0125M-$C_6H_3F(NO_2)_2$; 30°.

Time (mins.)	926	1403	2383	2836	3822	5692
Decompn., %	24·24	31·84	46·24	49·76	58·08	67·04
10^4k	2·07	1·94	1·94	1·83	1·78	1·59

Mean $k = 1{\cdot}86 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

Mean deviation from mean 6·7%.

Except for the amine hydrofluorides (where solubilties were too low) $a = 4b$, ensuring that, so far as possible, the results are comparable with those of Singh and Peacock. It was not possible to work at the same absolute concentrations, owing to the high rates of the reactions under investigation.

Detailed results are given above for a few cases (Table II), and all the results are summarised in Table III. The mean deviation from the mean is always less than 3%, except for *m*-bromoaniline

hydrofluoride (about 6%). In this case the values of k fall with time and it is evident that a simple second-order law is not obeyed over the whole reaction. However, the rate over the first 50% of the reaction is nearly as large as that of the reaction with *m*-bromoaniline.

TABLE III.

Amine	a	b	$10^4k_{0\cdot1}$	10^4k_{10}	10^4k_{25}	10^4k_{50}	10^4k_{40}	E (cals.)	$\log_{10}A$
Aniline	0·05	0·0125	27·1	60·1	72·0	85·7	122	6400	2·55
	0·025	0·0125	—	—	—	85·5	—	—	—
	0·05	0·025	—	—	—	88·7	—	—	—
m-Toluidine	0·05	0·0125	—	99·2	—	142	203	6550	2·88
p-Chloroaniline	0·05	0·0125	—	6·39	—	10·0	15·5	8100	2·82
p-Bromoaniline	0·05	0·0125	—	4·57	—	7·25	11·1	8100	2·69
m-Chloroaniline	0·05	0·0125	—	1·37	—	2·24	3·54	8700	2·60
m-Bromoaniline	0·05	0·0125	—	1·27	—	2·06	3·21	8500	2·43
	0·025	0·0125	—	—	—	2·04	—	—	—
	0·05	0·025	—	—	—	2·09	—	—	—
Aniline hydrofluoride	0·025	0·0125	—	—	—	—	114	—	—
m-Bromoaniline hydrofluoride	0·025	0·0125	—	—	—	1·85	—	—	—

a and b are initial (molar) concentrations of amine and fluorodinitrobenzene respectively.
Mean values of k are from several experiments. k and A are l. mole^{-1} sec.$^{-1}$.

DISCUSSION.

Velocity coefficients and Arrhenius parameters for the reactions of the corresponding fluoro-, chloro-, and bromo-compounds are assembled in Table IV. The results of Singh and Peacock, of Rheinlander, and of van Opstall have been recalculated in terms of mole/l. and seconds, and for 50° where necessary. Our own results have also been extrapolated to 50°, the only temperature used by Rheinlander. Different authors have used slightly different solvents: we have used 99·8% (by wt.) ethanol, Rheinlander 99·16% (by vol.). Changes in water content in the medium of less than 1% do not increase velocity coefficients by more than 10% and only Rheinlander's results need correction on this account. Minor inconsistencies also arise because of varying initial concentrations, but neither these nor the solvent differences alter the main features of the assembled results.

TABLE IV.

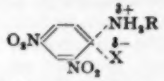
Amine	1-Fluoro-2 : 4-dinitrobenzene			1-Chloro-2 : 4-dinitrobenzene			1-Bromo-2 : 4-dinitrobenzene			1-Iodo-2 : 4-dinitrobenzene
	10^4k_{50}	E	$\log_{10}A$	10^4k_{50}	E	$\log_{10}A$	10^4k_{50}	E	$\log_{10}A$	10^4k_{50}
Aniline	168	6400	2·55	2·69	11,200	4·0	4·05	11,200	4·2	—
	—	—	—	2·74	10,400	3·5	—	—	—	—
	—	—	—	2·98	—	—	4·51	—	—	1·31
m-Toluidine ...	282	6550	2·88	3·91	11,600	4·4	5·59	11,600	4·6	—
				3·72	10,800	3·9	—	—	—	—
p-Chloroaniline	23·1	8100	2·82	0·632	12,300	4·1	—	—	—	—
p-Bromoaniline	16·6	8100	2·69	0·544	14,600	5·6	—	—	—	—
m-Chloroaniline	5·46	8700	2·60	0·197	13,000	4·1	—	—	—	—
m-Bromoaniline	4·90	8500	2·43	0·219	15,100	5·5	—	—	—	—

k and A in 1 mole^{-1} sec.$^{-1}$. E in cals. (accurate to $\pm$ 500 cals.).
A is accurate to $\pm$0·3 unit.
Singh and Peacock (*loc. cit.*) used a = 0·4M., b = 0·1M. in absolute ethanol.
Van Opstall (*loc. cit.*) used a = 0·08M., b = 0·04M. in absolute ethanol.
Rheinlander (*loc. cit.*) used a = 0·1M., b = 0·1M. in 99·16% (by vol.) ethanol.
(a and b have the same significance as in Table II.)

The first major difference between the fluoro-compound and the other halides lies in the stoicheiometry of the reaction. Whereas the fluoro-compound consumes only one mole of amine per mole, the others consume two moles by virtue of the formation of stable salts by the hydrogen halide generated. The amine hydrofluorides may be ethanolysed under our experimental conditions, or it may be that they are readily dissociated hydrogen-bonded complexes rather than true salts. Whatever their nature, the critical fact is that they appear to react almost as readily with 1-fluoro-2 : 4-dinitrobenzene as do the free amines. This is exemplified in Table I. Moreover the reactions obey the rate law $dx/dt = k_2(a - x)(b - x)$ much better than the law $dx/dt = k_2(a - 2x)(b - x)$.

Inspection of Table IV reveals that for the reactions of these amines with the chloro- and bromo-compounds, the Arrhenius parameters are the same within experimental error, but for

the reactions of the fluoro-compound both the experimental energy of activation, E, and the non-exponential term, A, are strongly diminished, *viz.*, by about 5000 cals. and 10^{12}—10^{20} units respectively. The velocity coefficients for the reactions of the fluoro-compound are some 20—70 times greater than for the other halides, and it is clear that the diminution in A is more than offset by the increase in $e^{-E/RT}$. If it is assumed for the present that the reaction pursues a simple bimolecular course (cf. Brady and Cropper, *loc. cit.*) corresponding directly to second-order kinetics, the dipolar transition state may be represented by :



(X = F, Cl, or Br)

We may deduce that the relatively low values of A (low values of the entropy of activation) are caused mainly by an increase of solvation in the transition state relative to the uncharged initial state, and that this increase is most marked when X = F (cf. Bell, *J.*, 1943, 632). Thus it is solvation that makes possible the remarkably low energy of activation observed with the fluoro-compound. Moreover, the increased reaction velocity in aqueous ethanol, a solvent of higher " solvating power " than pure ethanol, is readily understood in terms of Hughes and Ingold's theory of solvent action (*Trans. Faraday Soc.*, 1941, **37**, 608). This critically important increased solvation of the transition state is readily intelligible in terms of the small size of the fluoride ion and its comparatively large solvation energy. Thus the ionic radii of the fluoride, chloride, and bromide ions are 1·36, 1·81, and 1·95 Å respectively (Pauling, " The Nature of the Chemical Bond," Ithaca, 1945, p. 346). The heats of solution of fluoride, chloride, and bromide ions in water are 97,000, 65,000, and 57,000 cals./g.-ion respectively (Bernal and Fowler, *J. Chem. Physics*, 1933, **1**, 538). Mishchenko (*Acta Physicochim. U.R.S.S.*, 1935, **3**, 693) has shown that the heats of solution of ions in methanol and ethanol are of the same order as in water, so we may take Bernal and Fowler's values as giving an approximate measure of the different solvation energies (cf. A. G. Evans, *Trans. Faraday Soc.*, 1946, **42**, 724). The sharp divergence of behaviour between the fluoro-compound and other halides should be much less marked in weakly solvating solvents, but more marked in strongly solvating solvents, a subject which we hope to investigate in due course.

Berliner, Quinn, and Edgerton (*J. Amer. Chem. Soc.*, 1950, **72**, 5305) have suggested that reactions of the 1-halogeno-2-nitro- and 2-halogeno-1-nitro-naphthalenes, very similar to those at present under discussion, occur by a two-stage mechanism :

$$RX + NHR'_2 \rightleftharpoons \text{Complex} \quad \text{(i)}$$

$$\text{Complex} \longrightarrow NRR'_2 + X^- \quad \text{(ii)}$$

where X = Cl or Br. These authors studied pseudo-unimolecular reactions, using piperidine both as reagent and solvent. Consequently their results yield no information about how the rate of reaction depends on the concentration of piperidine. However, the results recently published by us (Chapman, Parker, and Soanes, *loc. cit.*) for *o*- and *p*-halogenonitrobenzenes make it very probable that the reactions studied by Berliner *et al.* would show second-order kinetics under suitable conditions.

The complex in equation (i) is formulated as in Fig. 1, with apparently a true covalency between N and $C_{(1)}$. A proton must also have been lost from the nitrogen, but this is not likely to have kinetic significance. This formulation presents certain steric difficulties. It requires that the nitro-group shall be coplanar with the rings. With picryl iodide it is known (Huse and Powell, *J.*, 1940, 1398) that the *o*-nitro-group is nearly perpendicular to the ring, and with other *o*-halogenonitrobenzenes or 1-halogeno-2-nitro- or 2-halogeno-1-nitro-naphthalenes, geometrical considerations make a similar conclusion probable, although there appears to be no critical experimental evidence available. To the extent that the nitro-group is not coplanar with the ring, it will be " imperfectly conjugated " with the ring, thus raising the energy of the complex. In the formation of complexes between *o*-chloronitrobenzene or 1-chloro-2 : 4-dinitrobenzene and aromatic amines, the weight of evidence seems to be against covalent-bond formation (cf. Hammick *et al.*, *J.*, 1940, 1539). There seems to be no positive evidence for such bond formation with piperidine, nor apparently has any such complex been isolated.

Berliner *et al.* assume that " the formation of the intermediate is probably a rapid process," with " the breaking of the carbon–halogen bond the slow, rate-determining step." If, as seems probable, these reactions would show second-order kinetics in dilute solution, then the first step would under these conditions also be reversible, and be in fact reversed. However, in an excess of piperidine the first step may go rapidly to completion and not in fact be reversed. In

this case the second step would be truly rate-determining. In the former case the overall rate would be determined by the velocity of the second step and the position of equilibrium in the first step. The ready displacement of fluorine might then be ascribed to its great electronegativity and consequent ease of anionisation. The following considerations seem to us, however, to cast grave doubts on the two-stage mechanism.

A second nitro-group in the *ortho*- or *para*-position to the halogen in *o*- or *p*-halogenonitrobenzene or 1-halogeno-2- or -4-nitronaphthalene greatly facilitates nucleophilic displacement of the halogen. Thus in the benzene series, reactions of piperidine with *o*- and *p*-chloronitrobenzene in dilute solution in 99·8% ethanol have been shown in these laboratories (Chapman *et al.*, *loc. cit.*) to have energies of activation of ~18,000 cals. whereas the corresponding value for 1-chloro-2 : 4-dinitrobenzene is ~10,000 cals. (Brady *et al.*, *loc. cit.*). The entropy factors differ very little. In the naphthalene series van Opstall (*Rec. Trav. chim.*, 1933, **52**, 901) has shown that 1-chloro-2 : 4-dinitronaphthalene reacts with amines about 200 times as fast as 1-chloro-2 : 4-dinitrobenzene, which itself reacts faster than 1-chloro-2-nitro- or 2-chloro-1-nitro-naphthalene with piperidine. An electron-withdrawing group such as NO_2 could hardly act by facilitating ionisation of the halogen. In our view it almost certainly acts by diminishing the repulsive energy between the attacking nucleophilic reagent and the halogeno-compound (cf. Glasstone, Laidler, and Eyring, " Theory of Rate Processes," New York, 1941, pp. 452 *et seq.*) in a typical bimolecular process. It seems to us, therefore, that even in the presence of an excess of piperidine, stage (ii) in Berliner's mechanism cannot be truly rate-determining. We may add that Lindemann and Pabst (*Annalen*, 1928, **462**, 24) have provided convincing experi-

FIG. 1.

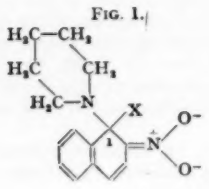
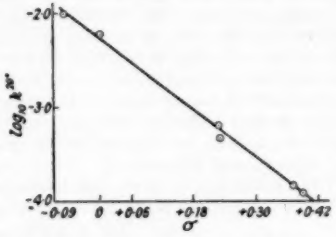


FIG. 2.



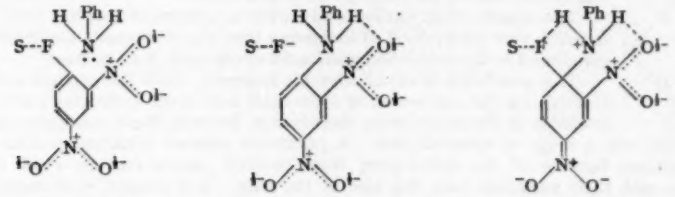
mental evidence that, in the reactions of 1-chloro-2 : 4-dinitrobenzene with aromatic amines, where complexes can be isolated, such complexes are not intermediates in the reaction. In these circumstances we prefer, for our own reactions, a one-stage bimolecular substitution process, with the probability that this mechanism is universal for this class of reaction (cf. Brady *et al.*, *loc. cit.*). The Arrhenius parameters of the reactions may be qualitatively understood, as we have seen, in terms of such a mechanism and the structure of the corresponding transition state.

Despite the existence of a bulky nitro-group *ortho* to the seat of substitution it is unlikely that steric compression energies contribute to the observed energies of activation. Preliminary calculations on a reasonable model of the transition state (Chapman, to be published) show that such compressions are small and vary little with change of halogen. It is true that they are least when fluorine is the halogen. Also the conjugation (p. 3305) of the *o*-nitro-group with the ring will be at a maximum when the halogen is fluorine, because of its small size. Both these factors may facilitate the reaction.

We have also considered the possibility that variation in the dipole–dipole interaction energy may be responsible for the observed variations in E as the halogen is varied. However, the dipole moments of 2 : 4-$(NO_2)_2C_6H_3X$ vary very little: μ = 3·5, 3·0—3·3, and 3·1 ± 0·1D when X = F, Cl, and Br respectively (*Trans. Faraday Soc.*, 1934, **30**, lxxviii). It does not seem likely that the equilibrium distance between the dipoles in the transition state, to which the interaction energy is very sensitive, will differ very greatly according to the nature of X, being largely determined by the structures of the reacting molecules as a whole. We therefore conclude tentatively that dipole–dipole interaction does not alter very much in the different reactions under consideration.

Fig. 2 shows that, as for the chloro- and bromo-compounds, these reactions of the fluoro-compound obey to a fair degree of approximation the Hammett σ–ρ relation (Hammett,

" Physical Organic Chemistry," New York, 1941, p. 184). The straight line has a slope −4·245 for 20°, and similar lines have slopes −4·180 for 30°, and −4·006 for 40°, thus defining the ρ values for this reaction for these three temperatures. The variation of velocity coefficients with the structure of the amine, a subject in which we are not primarily interested here, is broadly in accordance with expectations based on their structure and basic strength. In our view, a formula of the intermediate complex of the type suggested by Berliner *et al.* represents one extreme configuration of the transition state, which may be specified as a hybrid of several configurations, thus :



We include a proton in our formulation but the loss of it is kinetically insignificant. We have deliberately excluded *o*-quinonoid stuctures because of doubts about the coplanarity of the *o*-nitro-group with the ring. We also include, in our formulation of the transition state, electrostatic interactions (represented by broken lines) between (*a*) amino-hydrogen and nitro-oxygen, (*b*) amino-hydrogen and fluorine, and (*c*) fluorine and solvent (S represents several solvent molecules). We specify the solvent interaction to be with fluorine because of its special importance for this case, although we envisage the whole of the transition state as being solvated. It seems to us that there can be little doubt of the operation of this solvation factor : factors (*a*) and (*b*) we put forward more tentatively (cf. a similar suggestion by Gold and Whittaker, *J.*, 1951, 1188, for electrophilic substitution) and hope to devise experiments to test these ideas. Factor (*a*) could operate whatever the halogen, whereas factor (*b*) would only be expected to be appreciable when the halogen is fluorine. The latter, therefore, may be an additional factor (besides the increased solvation discussed above) tending to produce a lower energy and entropy of activation for the fluoro-compound.

We hope to extend this work to include *p*-fluoronitrobenzene and 1-fluoro-2 : 4-dinitronaphthalene and possibly fluoromononitronaphthalenes, as well as giving attention to variation of solvent.

We thank the Chemical Society for a grant for the purchase of materials, and the Royal Society for a grant for apparatus.

UNIVERSITY COLLEGE, SOUTHAMPTON. [*Received, July 14th*, 1951.]

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730. *Infra-red Studies of the Molecular Interactions of ω-Hydroxypalmitic Acid.*

By W. J. ORVILLE THOMAS.

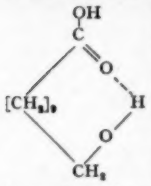
The end-group interactions of ω-hydroxypalmitic acid in carbon tetrachloride solutions have been studied spectroscopically. No indications of the cyclisation of the monomeric species have been obtained.

Values for the extinction coefficient of the hydroxyl bands of ethyl alcohol and propionic acid at 59° in carbon tetrachloride have been obtained.

THE effects of association on the infra-red absorption spectrum of carboxylic acids in solution have been examined many times (cf. Davies and Sutherland, *J. Chem. Physics*, 1938, **6**, 755). It has been shown that under suitable experimental conditions certain bands consisted of two components, one due to the monomeric and the other to the associated form of the molecule. Careful quantitative work by Kempter and Mecke (*Z. physikal. Chem.*, 1941, *B*, **46**, 229) and

Hoffmann (*ibid.*, 1943, *B*, **53**, 185) has shown that for the alcohols the monomeric molecules alone contribute to the " free " OH absorption band.

Davies and Sutherland (*J. Chem. Physics*, 1938, **6**, 767) studied typical alcohols and carboxylic acids in solution and showed that the groups CH_2·OH and CO_2H when free, could be separately identified and quantitatively estimated. Even when the two groups were present in the same molecule it was possible to follow the frequency of occurrence of the free ·CH_2·OH and CO_2H groups (Davies, *J. Chem. Physics*, 1938, **6**, 770). This is possible because the characteristic hydroxyl absorption for alcohols is at 2·76 μ whilst that for the carboxyl group is at 2·84 μ.



The results of an earlier study with ω-hydroxyundecanoic acid (Davies, *loc. cit.*) were interpreted as indicating that the monomeric molecules of this compound in dilute solution assumed a cyclic form (*e.g.*, as inset).

This possibility is of considerable interest. Both the entropy and energy changes for the conversion of open-chain into cyclic molecules would become available if the equilibrium distribution between these configurations could be evaluated over a range of temperatures. A particular interest attaches to such data in these structures because of the well-known Ruzicka–Stoll results on the yield of cyclic esters, etc., and their variation with the size of the ring. The present equipment, and in particular the greatly increased stability in recording spectra, suggested that the earlier observations should be confirmed and extended if possible.

Experimental.

Materials and Experimental Cells.—" AnalaR " carbon tetrachloride was distilled from and kept over anhydrous silica gel; absolute ethyl alcohol was dried over anhydrous silica gel and a middle fraction collected on redistillation.

Dr. E. M. Wilkinson furnished a sample of carefully purified propionic acid. The hydroxypalmitic acid used was provided by Dr. M. Stoll of Firmenich et Cie, Geneva, whom we thank for this gift. The acid had m. p. 80—82°.

Solutions were prepared at the working temperature. With the dilute solutions used in this work path lengths of up to 40 mm. were necessary. The very simple cell illustrated in Fig. 1 was used. *H* is a heating coil, *F* a filling hole, *W* a rock-salt window, *S* a securing screw, *T* a small cavity for the insertion of a copper–constantan thermocouple junction, and *C* a spacing collar whose size can be varied from 1 mm. to 40 mm. It was found that the temperature could be controlled and read to ± 1°.

When necessary the moisture content of the spectrometer could be decreased and kept at a constant level by means of a stream of dry nitrogen in conjunction with silica gel as drying agent inside the instrument. A fused silica prism was used in the spectrometer for these experiments.

Experimental Procedure.—Since the Grubb-Parsons S.3 spectrometer is a single-beam instrument it is necessary to carry out two separate runs; one with solvent to obtain the background transmission (I_β) and the other with the working solution (I_a). Curves of $\log_{10} I_\beta/I_a$ against wave-length were plotted and the areas enclosed by the sharp bands and the peak heights determined. Then,

$$\log_{10} I_\beta/I_a = kc_m l \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where k is the extinction coefficient, c_m is the monomer concentration in g.-mol./l., and l the cell-length in cm. The expression on the left of equation (1), evaluated for the peak optical density, P, gives:

$$k_p = P/c_m l \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

An alternative measure, which is preferable on some grounds, and which we have also used, is the integrated intensity:

$$\int \log_{10} (I_\beta/I_a) d\omega \equiv A = c_m k_A l \Delta\omega$$

or

$$k_A = A/c_m l \Delta\omega \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $\Delta\omega$ is the half-width of the band in cm.$^{-1}$. Equations (2) and (3) give the value of the extinction coefficient when c_m is known. The values were determined graphically by counting squares in an appropriate plot. Much the greatest uncertainty in this procedure consisted in the base-line drawn to represent any background absorption: errors are liable to enter owing to the variable absorptions of water in the background and the overlapping of the adjacent hydroxyl bands, *i.e.*, of the sharp monomer peaks and the broader association bands which soon appear as the concentration is raised. As being perhaps the least arbitrary procedure the base-line was obtained by joining the points of minimum absorption on either side of the sharp bands.

On these simple grounds it is seen that the peak height P, or integral absorption A, should provide a measure of the monomer concentration, c_m, provided the extinction coefficient, k, does not vary with concentration and temperature. It is, however, necessary to know the value of the extinction coefficient, k, for the particular band in question. Thermodynamic data are available for solutions of propionic acid in carbon tetrachloride (Davies, Jones, Patnaik, and Moelwyn-Hughes, *J.*, in the press) which

enable the monomer concentration of propionic acid to be calculated under varying experimental conditions. The peak height and integral absorption of the hydroxyl band were obtained for propionic acid solutions of differing concentrations. Curves of peak height (P) and integral absorption (A) against monomer concentration (c_m) were drawn. Straight lines were obtained whose slopes gave a measure of the extinction coefficient, k', for the hydroxyl band of the carboxyl group of propionic acid.

The alcoholic OH band was calibrated by means of the hydroxyl band of ethyl alcohol. The peak heights and integral absorption of solutions so dilute that only the monomer was present were obtained and plotted against the concentrations, c, of the ethyl alcohol solutions. Over a certain range a straight

FIG. 1.

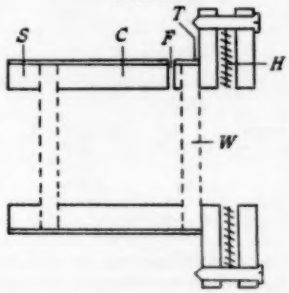


FIG. 2.

Peak height–monomer concentration curves for propionic acid and ethyl alcohol at 59°.

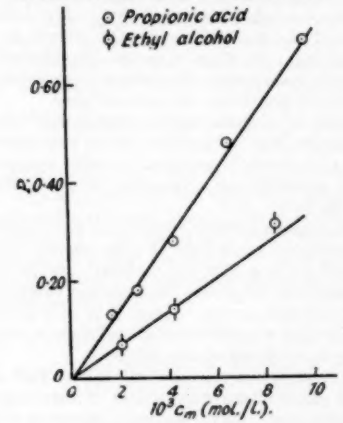
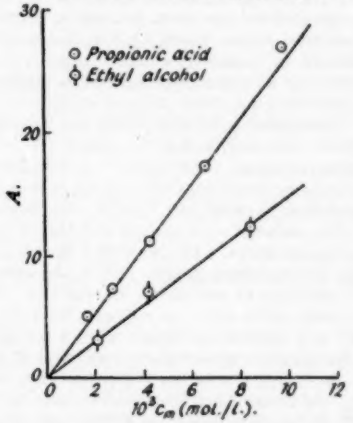


FIG. 3.

Integral absorption–monomer concentration curves for propionic acid and ethyl alcohol at 59°.



line was obtained, the slope of which gives a measure of the absorption coefficient, k'', for the OH band of the $\cdot CH_2 \cdot OH$ group.

The assumption is now made that the absorption coefficients of the free hydroxyl groups present in monomeric ω-hydroxypalmitic acid have the values k'' and k'. The quantitative accuracy of this assumption is somewhat uncertain but relatively correct results should be obtained. By this means the peak heights and integral absorptions obtained for the free hydroxyl bands of the hydroxy-acid were converted directly into measurements of the monomer concentrations of these two groups. The measurements were conducted to as low a concentration as was reasonable ($5{\cdot}0 \times 10^{-4}$M) with the practical errors involved.

RESULTS.

The curves of peak height, P, and integral adsorption, A, against monomer concentration, c_m, for propionic acid and ethyl alcohol are given in Figs. 2 and 3. The results obtained for ω-hydroxypalmitic acid are given in Tables I and II (in which l is the cell length, and c_m is the monomer concentration, estimated spectroscopically, of the free hydroxyl groups at the total concentration c g.—mol./litre).

From equations (2) and (3) the values of the extinction coefficients for propionic acid and ethyl alcohol may be obtained. They are: propionic acid, k_p 70 ± 2, k_A 73 ± 2; ethyl alcohol, k_p 37 ± 2, k_A 39 ± 2.

TABLE I.

The alcoholic OH *absorption in carbon tetrachloride solutions of ω-hydroxypalmitic acid at* 62·4° ± 1°

Molar concn., 10^3c	A/l	Monomer concn., 10^3c_m	$10^3c_m/c$	Molar concn., 10^3c	A/l	Monomer concn., 10^3c_m	$10^3c_m/c$
0·956	1·444	1·00	105	2·390	3·570	2·50	105
1·338	1·802	1·25	93	5·976	8·301	5·80	97

TABLE II.

The carboxylic OH *absorption in carbon tetrachloride solutions of ω-hydroxypalmitic acid at* 62·4° ± 1°.

Molar concn., 10^3c	A/l	Monomer concn., 10^3c_m	$10^3c_m/c$	Molar concn., 10^3c	A/l	Monomer concn., 10^3c_m	$10^3c_m/c$
0·956	2·802	1·00	105	2·390	5·811	2·06	86
1·338	3·573	1·26	94	5·976	10·22	3·63	61

DISCUSSION.

It was earlier considered (Davies and Sutherland, *loc. cit.*), that the extinction coefficient, k, might vary both with temperature and with monomer concentration, c_m; the results obtained during this work, however, indicate that, over the limited concentration range studied, k does not vary with c_m for propionic acid or ethyl alcohol.

The results obtained for the hydroxy-acid indicate that the percentage concentration of free CH_2·OH groups remains constant in the concentration range studied. The value obtained for the percentage monomer present is, within the accuracy of the method, 100%. The latter theoretical figure would be obtained only if (*a*) none of the alcoholic hydroxyl groups were involved in association, either inter- or intra-molecularly; (*b*) there were no experimental errors; or (*c*) the correct extinction coefficients for the hydroxy-acid absorptions were known. Within the limitations imposed by (*b*) and (*c*), we can regard condition (*a*) as established.

The accuracy of this study can reasonably be taken to surpass that of the earlier work (Davies, *loc. cit.*), and so to correct the previous conclusion that cyclisation of the monomeric molecules occurs. This negative result, however, cannot be generally extended to other solvents and solutes, but it is of importance in view of the earlier infra-red and some recent *X*-ray studies in solution (Kratky and Worthmann, *Monatsh.*, 1946, **76**, 263).

The value of c_m/c for the OH band of the carboxyl group increases steadily as the concentration decreases. This indicates the breakdown of associated complexes to give simpler units with free carboxyl groups. Over the measured range it is clear that the carboxyl groups are still involved in associative interaction. This is perhaps not surprising, as they are certainly far more liable to be so engaged than the alcoholic hydroxyl groups. Thus it is difficult to draw any precise conclusion as to a possible cyclisation from the carboxyl group data, except in the negative confirmatory sense that it does not serve to establish such a feature.

Accepting the earlier indication that the alcoholic hydroxy-groups are not taking part in any interaction, then the simplest basis for the carboxyl group interactions would be a monomer $\rightleftharpoons$ dimer equilibrium in which they alone are participating. Quantitatively, however, this assumption is not substantiated by the "constant" $k_{eq.} = 2c\alpha^2/(1-\alpha)$, estimated as 0·041, 0·026, 0·011, for solutions 10^3c = 1·338, 2·390, and 5·976 respectively. It is evident that the process is more complex than that suggested above.

Further detailed study at lower concentrations and higher temperatures is evidently needed for the elucidation of the molecular interactions of ω-hydroxypalmitic acid in dilute solution. Probably a more fruitful approach would be to use a polar solvent where the degree of association would be less at concentrations comparable with those studied here.

This problem was suggested by Dr. Mansel Davies to whom I am grateful for much useful discussion.

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[*Received, May 23rd,* 1951.]

731. *A Novel Method of Cyanoethylation.*

By L. Bauer, J. Cymerman, and (in part) W. J. Sheldon.

2-Diethylaminoethyl cyanide (II) behaves as a Mannich base in undergoing both amine-elimination and amine-exchange reactions, the amine-exchange reaction with arylamines providing a convenient route to the difficultly accessible *N*-arylcyanoethylamines, *e.g.* *N*-2-cyanoethyl-*p*-anisidine. The reaction is shown to be acid-catalysed, and a mechanism is proposed which accounts satisfactorily for the experimental results.

Cyanoethylation of primary and secondary amines is usually achieved by addition of vinyl cyanide, often in the presence of an acidic or basic catalyst (Bruson, *Org. Reactions*, **1949**, **5**, 79; Saunders, *Ann. Reports*, **1948**, **45**, 124; Bayer, *Angew. Chem.*, **1949**, **61**, 229). This method gives positive results with primary and secondary aliphatic and saturated cyclic amines, but is unsatisfactory for aromatic amines (Whitmore, Mosher, Adams, Taylor, Chapin, Weisel, and Yanko, *J. Amer. Chem. Soc.*, **1944**, **66**, 725; B.P. 466,316; Elderfield, Gensler, Bembry, Kremer, Brody, Hageman, and Head, *J. Amer. Chem. Soc.*, **1946**, **68**, 1262; Cookson and Mann, *J.*, **1949**, 67).

It is known that Mannich bases (Blicke, *Org. Reactions*, **1942**, **1**, 303) such as (I) and their salts will readily undergo either amine elimination to give diethylamine and an ethylenic compound (reaction 1*a*, 1*b*) (Mannich and Honig, *Arch. Pharm.*, **1927**, **265**, 598; Mannich and Heilner, *Ber.*, **1922**, **55**, 356; Mannich, Koch, and Barkousky, *ibid.*, **1937**, **70**, 355; cf. Du Feu, McQuillin, and Robinson, *J.*, **1937**, 53; Snyder, Smith, and Stewart, *J. Amer. Chem. Soc.*, **1944**, **66**, 200; Snyder and Speck, *ibid.*, **1939**, **61**, 668) or amine exchange (reaction 2*a*, 2*b*) (Snyder and Brewster, *J. Amer. Chem. Soc.*, **1948**, **70**, 4230; Snyder and Eliel, *ibid.*, **1948**, **70**, 4233; Hultquist *et al.*, *ibid.*, **1948**, **70**, 23; cf. Howe, Zambito, Snyder, and Tishler, *ibid.*, **1945**, **67**, 38; von Braun, Kuhn, and Goll, *Ber.*, **1926**, **59**, 2330).

2-Dialkylaminoethyl cyanides, such as (II), obtained in high yield by cyanoethylation of aliphatic amines, are known to dissociate into their precursors on prolonged heating (Whitmore *et al.*, *loc. cit.*; Hoffmann and Jacobi, U.S.P. 1,992,615) by an elimination reaction (reaction 3*a*, 3*b*), which is due to the easy removal of a hydrogen atom from the α-carbon atom as a

$$\underset{\text{(I)}}{RCO\cdot CH_2\cdot CH_2\cdot NEt_2} \qquad \underset{\text{(II)}}{CN\cdot CH_2\cdot CH_2\cdot NEt_2} \qquad \underset{\text{(III)}}{CN\cdot CH_2\cdot CH_2\cdot \overset{+}{N}MeEt_2)\bar{I}}$$

proton by the influence of the neighbouring electron-attracting cyanide and carbonyl groups. It is known that, for example, an " onium " salt may undergo simultaneously both elimination and substitution reactions (Hughes and Ingold, *Trans. Faraday Soc.*, **1941**, **37**, 657); it was thought possible, therefore, that a corresponding amine-exchange reaction might occur also in the case of the dialkylaminoethyl cyanides (reaction 4*a*, 4*b*), and that, if R = aryl or substituted aryl, a means of obtaining the difficultly-accessible cyanoethylated aromatic amines would be at hand.

$$RCO\cdot CH_2\cdot CH_2\cdot NEt_2 \longrightarrow RCO\cdot CH{:}CH_2 + NHEt_2 \quad (1a)$$

$$RCO\cdot CH_2\cdot CH_2\cdot \overset{+}{N}HEt_2)\bar{X} \longrightarrow RCO\cdot CH{:}CH_2 + \overset{+}{N}H_2Et_2)\bar{X} \quad (1b)$$

$$RCO\cdot CH_2\cdot CH_2\cdot NEt_2 + NHR_1R_2 \longrightarrow RCO\cdot CH_2\cdot CH_2\cdot NR_1R_2 + NHEt_2 \quad (2a)$$

$$RCO\cdot CH_2\cdot CH_2\cdot \overset{+}{N}HEt_2)\bar{X} + NHR_1R_2 \longrightarrow RCO\cdot CH_2\cdot CH_2\cdot NR_1R_2 + \overset{+}{N}H_2Et_2)\bar{X} \quad (2b)$$

$$CN\cdot CH_2\cdot CH_2\cdot NEt_2 \longrightarrow CN\cdot CH{:}CH_2 + NHEt_2 \quad (3a)$$

$$CN\cdot CH_2\cdot CH_2\cdot \overset{+}{N}HEt_2)\bar{X} \longrightarrow CN\cdot CH{:}CH_2 + \overset{+}{N}H_2Et_2)\bar{X} \quad (3b)$$

$$CN\cdot CH_2\cdot CH_2\cdot NEt_2 + RNH_2 \longrightarrow CN\cdot CH_2\cdot CH_2\cdot NHR + NHEt_2 \quad (4a)$$

$$CN\cdot CH_2\cdot CH_2\cdot \overset{+}{N}HEt_2)\bar{X} + RNH_2 \longrightarrow CN\cdot CH_2\cdot CH_2\cdot NHR + \overset{+}{N}H_2Et_2)\bar{X} \quad (4b)$$

Reaction of anilinium benzenesulphonate with (II) at 180° for 1 hour gave 50% of the required 2-cyanoethylaniline (m. p. 51—52°) (Cookson and Mann, *loc. cit.*). However, reaction of (II) with aniline either at 180° or at 200° for 1 hour gave a quantitative recovery of the starting-materials. The reaction thus appears to be acid-catalysed. The benzenesulphonate of (II) was found to be extremely hygroscopic; however the action of methyl iodide on (II) readily gave the quaternary iodide (III); reaction of this with aniline at 180° for 1 hour gave 50% of 2-cyanoethylaniline.

Amine exchange in Mannich bases takes place with either the base (reaction 2*a*) or the salt (2*b*), and probably proceeds by amine elimination (reaction 1*a* or 1*b*) followed by a Michael addition to the activated ethylenic linkage (cf. Snyder and Brewster, *J. Amer. Chem. Soc.*, **1944**, **66**, 200), since it is recorded only in the case of aliphatic and saturated cyclic bases which are known to add readily to vinyl cyanide under mild conditions (Whitmore *et al.*, *loc. cit.*) in contrast to aromatic amines. The occurrence of amine exchange in a substance which cannot react by amine elimination followed by amine addition has been reported by Snyder and Eliel (*loc. cit.*) for 1-methylgramine where it takes place readily if the salt (hydrochloride or methiodide) is used, but not with the free base alone under any conditions. The reaction is thus an acid-catalysed substitution reaction (cf. Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703).

Boron trifluoride, a Lewis acid, was as effective as a proton for this reaction. In the present method of cyanoethylation of aromatic amines, the reaction was also found to be acid-catalysed, and the following mechanism is therefore put forward (reactions 5, 3*b*, 6, and 7).

$$CN\cdot CH_2\cdot CH_2\cdot NEt_2 + \overset{+}{N}H_2Ar\}\bar{X} \longrightarrow CN\cdot CH_2\cdot CH_2\cdot \overset{+}{N}HEt_2\}\bar{X} + NH_2Ar \quad . \; . \; . \quad (5)$$

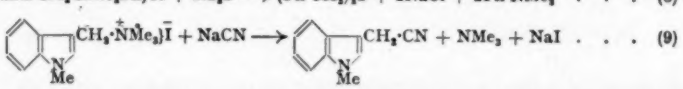
$$CN\cdot CH_2\cdot CH_2\cdot \overset{+}{N}HEt_2\}\bar{X} + NH_2Ar \longrightarrow NHEt_2 + CN\cdot CH_2\cdot CH_2\cdot \overset{+}{N}H_2Ar\}\bar{X} \quad . \; . \quad (6)$$

$$CN\cdot CH_2\cdot CH_2\cdot \overset{+}{N}H_2Ar\}\bar{X} + NHEt_2 \longrightarrow CN\cdot CH_2\cdot CH_2\cdot NHAr + \overset{+}{N}H_2Et_2\}\bar{X} \quad . \; . \quad (7)$$

Reaction (5) is a simple competition for the proton which is thereby transferred from the anilinium cation to the more strongly basic (II). The *N*-2-cyanoethyl-*NN*-diethylammonium ion is then able to react further by either reaction (3*b*), the elimination reaction, or with a molecule of arylamine (reaction 6), involving elimination of diethylamine and simultaneous reaction of arylamine to give the stable *N*-aryl-*N*-2-cyanoethylammonium ion. This then undergoes a further reaction (7) by which it loses its proton to the more basic diethylamine, giving the desired *N*-aryl-2-cyanoethylamine.

Displacements showing close similarity to reaction (6) have been reported; thus Snyder and Speck (*J. Amer. Chem. Soc.*, 1939, **61**, 668, 2895) and Snyder and Eliel (*ibid.*, 1948, **70**, 1703) respectively record that reactions (8) and (9) took place very readily.

$$2Ph\cdot CH_2\cdot \overset{+}{N}Me_2Ph\}\bar{C}l + Na_2S \longrightarrow (Ph\cdot CH_2)_2S + 2NaCl + 2Ph\cdot NMe_2 \quad . \; . \; . \quad (8)$$



(9)

It is seen that, whatever the relative rates of reactions (3*b*) and (6), there is formed one mol. of diethylammonium salt. That the reaction is a substitution and not an elimination followed by an addition reaction was also shown by the following experiment. Vinyl cyanide (1·5 mols.), diethylamine (1·5 mols.), and anilinium benzenesulphonate (1 mol.), heated at 180° for 1 hour, gave 77% of diethylammonium salt, evidently formed by the proton-exchange reaction (10), but only 2·5% of 2-cyanoethylaniline. The formation of this product must be ascribed to the formation, *in situ*, of some (II) (cf. Whitmore *et al.*, *loc. cit.*) from the amount of diethylamine (0·5 mol.) not consumed in reaction (10) followed, by the reaction (5) of (II) with such anilinium ion as had not undergone reaction (10), to give the *N*-2-cyanoethyl-*NN*-diethylammonium ion, which could then react further by either reaction (3*b*) or (6). Since a 50% yield of 2-cyanoethylaniline is normally obtained by this method, it follows that probably not more than about 5% of *N*-2-cyanoethyl-*NN*-diethylammonium ion was formed in the first instance, *i.e.* that about 95% of anilinium salt had reacted according to reaction (10).

$$Ph\cdot \overset{+}{N}H_3\}\bar{X} + NHEt_2 \longrightarrow Ph\cdot NH_2 + \overset{+}{N}H_2Et_2\}\bar{X} \quad . \; . \; . \; . \; . \quad (10)$$

In view of Snyder aud Eliel's findings (*loc. cit.*) that boron trifluoride was effective as an acid catalyst in the amine-exchange reaction of 1-methylgramine, a mixture of aniline and (II) was treated with boron trifluoride (1 mol.) at 180° for 1 hour, but this gave almost quantitative reovery of starting-materials. In view of the well-known tendency of boron trifluoride to co-ordinate with the cyanide group (cf. its use as a Friedel–Crafts catalyst), a similar experiment using 2 mols. of boron trifluoride was carried out, with the same negative result. This failure of boron trifluoride to function as an acid catalyst in the present reaction may possibly be ascribed to the much more electron-attracting nature of the aryl group in aniline, and of the 2-cyanoethyl group in (II), compared with the alkyl residues in dimethylamine and piperidine,

the two bases concerned in Snyder and Eliel's work (*loc. cit.*). This greater electron-attracting power may result in a reduced availability of the free electron-pair on the amino-nitrogen for co-ordination with boron trifluoride.

The extension of the present cyanoethylation reaction to other aromatic amines was next investigated. Reaction of (II) with 4-diphenylylammonium benzenesulphonate (Bauer and Cymerman, *J.*, 1950, 1826) at 200° for 1 hour gave 68% of diethylammonium salt and 50% of the required 4-2′-cyanoethylaminodiphenyl (m. p. 146°); some 4-aminodiphenyl was also formed in the reaction. Treatment of 4-diphenylylammonium benzenesulphonate with 2-morpholinoethyl cyanide at 200° for 1 hour similarly gave morpholinium benzenesulphonate, and a smaller yield of 4-2′-cyanoethylaminodiphenyl. This compound was also obtained by direct reaction of 4-aminodiphenyl and vinyl cyanide. Although treatment of 4-aminodiphenyl with vinyl cyanide in acetic acid at 170° for 4—6 hours under pressure, with and without copper acetate and/or copper powder catalysts, gave only 4-acetamidodiphenyl, repetition of the experiment in an autoclave at 150° for 4 hours, a reduced amount of acetic acid being used, gave a 13% yield of 4-2′-cyanoethylaminodiphenyl, isolated as the hydrochloride, identical with that of the sample prepared as described above.

Reaction of 4-chloroanilinium toluene-*p*-sulphonate, 2-naphthylammonium benzenesulphonate, *p*-methoxyanilinium benzenesulphonate, and diphenylammonium benzenesulphonate with (II) at 180—200° for 0·5—1 hour gave the required *N*-aryl-2-cyanoethylamine, recovered arylamine, and diethylammonium salt in the yields shown in the Table.

		% Yield of		
Arylammonium salt used	pK_a at 25° of arylamine	*N*-aryl-2-cyanoethylamine	arylamine	diethylammonium salt
p-Methoxyanilinium	5·29	69	21	78·5
Anilinium	4·58	50	19	77
4-Diphenylylammonium	4·27	50	—	68
2-Naphthylammonium	4·11	20·5	49	70·5
p-Chloroanilinium	4·0	20	25	49
Diphenylammonium	0·85	0, 0	62, 79	85, 73·5

A connection between the yields of 2-cyanoethylamines and the basic strengths (pK_a) of the parent amines (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469) is immediately apparent, and may indicate that reaction (6) involves co-ordination of the amino-nitrogen of the arylamine with the electron-deficient β-carbon atom of a carbonium cation. An increase in the electron-attracting properties of the aryl nucleus would then reduce the availability of the electron-pair for this co-ordination step, thus lowering the rate of reaction (6). Further work is in progress to confirm this hypothesis.

In one experiment with 2-naphthylammonium benzenesulphonate and (II), 3 : 4-6 : 7-dibenzacridine was obtained in 14% yield. The formation of this compound from 2-naphthylamine and formaldehyde is well known (Mohlau and Haase, *Ber.*, 1902, **35**, 4164; Ullmann and Fetvadjian, *ibid.*, 1903, **36**, 1027), and its isolation here presupposes the existence of formaldehyde in the reaction mixture; this can only have arisen from the decomposition of (II) into methyl cyanide, formaldehyde, and diethylamine—equivalent to the reversibility of the formation of certain Mannich bases (Mannich and Kather, *Arch. Pharm.*, 1919, **257**, 18; Mannich and Dannehl, *ibid.*, 1938, **276**, 206). Such an explanation may be feasible. This, and other implications of this cyanoethylation reaction, are receiving further investigation.

Experimental.

N-2-*Cyanoethyl*-*NN*-*diethyl*-*N*-*methylammonium Iodide*.—From the exothermic reaction of 2-diethylaminoethyl cyanide (6·3 g.) and methyl iodide (14 g., 2 mols.) in dry ether (25 c.c.) the quaternary *iodide* (9·5 g., 71%) was obtained as white crystals, m. p. 165° (decomp.) (Found: N, 10·05. $C_8H_{17}N_2I$ requires N, 10·4%).

2-*Cyanoethylaniline*.—(*a*) A mixture of anilinium benzenesulphonate (10 g.) and 2-diethylaminoethyl cyanide (8·5 g., 1·5 mols.) was heated at 180° for 1 hour. The cooled mixture was treated with ether, and the precipitate recrystallised from acetone, giving white needles (7 g., 77%) of diethylammonium benzenesulphonate, m. p. and mixed m. p. 138—139°.

Distillation of the ethereal filtrate afforded two fractions: (1) 2 g., b. p. 40—42°/0·05 mm., n_D^{19} 1·5072, a mixture of aniline and 2-diethylaminoethyl cyanide, which when boiled with acetic anhydride gave acetanilide (1 g.), m. p. 114° [corresponding to 0·7 g. (19%) of aniline]; (2) 2·85 g. (50%), b. p. 122—125°/0·05 mm., white needles, m. p. 51—52°, of 2-cyanoethylaniline (Cookson and Mann, *loc. cit.*, give b. p. 178—186°/16 mm., m. p. 51·5°).

(*b*) A mixture of *N*-2-cyanoethyl-*NN*-diethyl-*N*-methylammonium iodide (6·7 g.) and aniline (2·8 g., 1·2 mols.) was heated under reflux at 180° for 1 hour. Distillation gave two fractions: (1) 0·4 g.

(0·2 mol.), b. p. 45°/0·07 mm., recovered aniline; (2) 1·8 g. (50%), b. p. 126—130°/0·07 mm., prismatic needles, m. p. 50—52°, of 2-cyanoethylaniline.

(*c*) A mixture of 2-diethylaminoethyl cyanide (12·6 g.) and aniline (18·6 g., 2 mols.) was heated under reflux at 180° (200° in a second experiment) for 1 hour. Distillation gave only one fraction, b. p. 35—40°/0·05 mm. (30 g.). No residue remained.

(*d*) Similar results were obtained on addition of boron trifluoride–ether complex (1 or 2 mols.) to the reaction mixture

(*e*) Vinyl cyanide (3·2 g., 0·06 mol.), diethylamine (4·4 g., 0·06 mol.), and anilinium benzenesulphonate (10 g., 0·04 mol.) were heated under reflux at 180° for 1 hour. The cooled mixture on trituration with acetone gave white needles (6 g., 66%) of diethylammonium benzenesulphonate, m. p. and mixed m. p. 139°. The acetone filtrate on distillation gave two fractions: (1) 3·2 g., b. p. 35—40°/0·07 mm., n_D^{19} 1·4841, a mixture of aniline and 2-diethylaminoethyl cyanide, which when treated with acetic anhydride gave acetanilide (1 g.) [corresponding to 0·7 g. (19%) of aniline]; (2) 0·15 g. (2·5%), b. p. 120—125°/0·07 mm., m. p. 51—52°, of 2-cyanoethylaniline. The residue (2·8 g.) solidified, and on crystallisation from acetone gave white needles (1 g., 11%) of diethylammonium benzenesulphonate, m. p. and mixed m. p. 139°. A buff residue (1·5 g.) remained, m. p. 220—230°, insoluble in acetone, methanol, pyridine, chloroform, 2-ethoxyethanol, and nitrobenzene; this was not further investigated.

4-2′-*Cyanoethylaminodiphenyl*.—(*a*) A mixture of 2-diethylaminoethyl cyanide (6·3 g., 1·5 mols.) and 4-diphenylylammonium benzenesulphonate (11 g., 1 mol.) (Bauer and Cymerman, *J.*, 1950, 1826) was heated at 200° for 1 hour. The cooled mixture was dissolved in alcohol (charcoal); on cooling there separated 4-2′-*cyanoethylaminodiphenyl* (3·5 g., 50%), m. p. 143—144°, which gave, on recrystallisation from alcohol or benzene, shining plates, m. p. 146° (Found: C, 80·5, 81·3; H, 6·4, 6·3; N, 12·3, 12·4, 12·6. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·4; N, 12·6%). The hydrated *hydrochloride* crystallised from ethanol–ether in fine needles, m. p. 177—178° (Found: N, 10·1. $C_{15}H_{14}N_2Cl,H_2O$ requires N, 10·1%).

On dilution of the alcoholic filtrate from the reaction mixture with ether, diethylammonium benzenesulphonate (5·2 g., 68%), m. p. 135—137°, separated; it crystallised from acetone in needles, m. p. and mixed m. p. 138—139°. Treatment of the alcoholic–ethereal solution with benzenesulphonic acid gave 4-diphenylylammonium benzenesulphonate, crystallising from water in buff plates, m. p. and mixed m. p. 276—278°; the base, 4-aminodiphenyl, had m. p. 48—50°, mixed m. p. 50—52°.

(*b*) 2-Morpholinoethyl cyanide (7 g.) and 4-diphenylylammonium benzenesulphonate (11 g.) were heated at 200° for 1 hour. Extraction of the cooled mixture with *iso*propanol, dilution of the extract with ether, and crystallisation of the precipitate from acetone, gave *morpholinium benzenesulphonate*, m. p. 110—111° (undepressed on admixture with an authentic specimen), in lustrous scales (Found: C, 49·0; H, 6·2. $C_{16}H_{19}O_4NS$ requires C, 49·0; H, 6·1%).

A solution of 4-diphenylylammonium toluene-*p*-sulphonate (7 g., 1 mol.) in 2-morpholinoethyl cyanide (5·6 g., 2 mols.) was maintained at 134° for 2·25 hours, then at 160° for 0·25 and finally at 180° for 0·25 hour. The mixture was diluted with methanol, basified, and then extracted with chloroform. The residue obtained on removal of solvent was kept at 100°/20 mm. for several hours and then crystallised from carbon tetrachloride; it formed white plates, m. p. 140—142° undepressed on admixture with the material (m. p. 146°) obtained in (*a*).

(*c*) (Experiment by Mr. W. J. Sheldon.) A mixture of 4-aminodiphenyl (20 g.), vinyl cyanide (9 c.c.), and acetic acid (8 c.c.) was heated with copper powder (2 g.) and copper acetate (1 g.) in an autoclave for 4 hours at 150° (bath temp.). Distillation of the mixture gave a product (20·7 g.), b. p. 120—180°/0·085 mm., the ethereal extracts of which were saturated with dry hydrogen chloride; the precipitate obtained, on recrystallisation from alcohol–ether, gave white crystals of 4-2′-cyanoethylaminodiphenyl hydrochloride, m. p. 174—177° (4 g., 13%) undepressed on admixture with the material obtained in (*a*).

p-*Chloro*-N-2-*cyanoethylaniline*.—2-Diethylaminoethyl cyanide (9·5 g., 1·5 mols.) and *p*-chloroanilinium toluene-*p*-sulphonate (15 g., 1 mol.) were heated at 180° for 1 hour. The cooled mixture was treated with ether, and the precipitated solid crystallised from acetone, giving diethylammonium toluene-*p*-sulphonate (6·0 g., 49%), m. p. 88° undepressed on admixture with an authentic specimen. Distillation of the ethereal filtrate afforded three fractions: (1) b. p. 53°/0·05 mm., unchanged 2-diethylaminoethyl cyanide (2·5 g., 0·4 mols.); (2) b. p. 75°/0·05 mm., *p*-chloroaniline (1·5 g., 25%), m. p. and mixed m. p. 70—71°; (3) 1·8 g. (20%), b. p. 155—160°/0·05 mm., m. p. 70—71°. Crystallisation from light petroleum (b. p. 90—100°) gave white prismatic needles, m. p. 75·5—76°, of p-*chloro*-N-2-*cyanoethylaniline* (Found: C, 60·2; H, 5·3. $C_9H_9N_2Cl$ requires C, 59·8; H, 5·0%).

N-2′-*Cyanoethyl*-2-*naphthylamine*.—(*a*) 2-Diethylaminoethyl cyanide (12·6 g., 2 mols.) and 2-naphthylammonium benzenesulphonate (15 g., 1 mol.) were heated under reflux at 200° for 0·5 hour. The cooled mixture, on treatment with acetone, gave diethylammonium benzenesulphonate (8·1 g., 70·5%), m. p. and mixed m. p. 137—139°. The acetone filtrate on distillation afforded 2-diethylaminoethyl cyanide (6·3 g., 1 mol.), b. p. 100°/22 mm. The residue on trituration with 95% alcohol gave a pale yellow solid (2 g., 20·5%), m. p. 95—96°, which on crystallisation from light petroleum (b. p. 90—100°) afforded white hexagonal plates, m. p. 102°, of N-2′-*cyanoethyl*-2-*naphthylamine* (Found: C, 79·9; H, 6·3. $C_{15}H_{14}N_2$ requires C, 79·5; H, 6·15%). The residue (m. p. 90—92°) left on evaporation of the 95%-alcoholic filtrate crystallised from light petroleum (b. p. 60—90°), giving 2-naphthylamine (3·5 g., 49%), identified by m. p. and mixed m. p.

(*b*) 2-Diethylaminoethyl cyanide (9·5 g., 1·5 mols.) and 2-naphthylammonium benzenesulphonate (15 g., 1 mol.) were heated at 180° for 1 hour. Trituration of the cooled mixture with acetone gave diethylammonium benzenesulphonate (7·7 g., 69%), m. p. and mixed m. p. 138—139°. The residue left by evaporation of the acetone filtrate gave, on trituration with ether, 3 : 4-

6 : 7-dibenzacridine, m. p. 215—216° (1 g., 14%), as pale yellow needles, from chloroform–alcohol or aqueous acetone (Found : C, 89·6; H, 4·6; N, 5·3. Calc. for $C_{21}H_{13}N$: C, 90·25; H, 4·65; N, 5·05%). The m. p. was undepressed on admixture of the material with an authentic specimen (m. p. 215—215·5°), prepared by Senier and Goodwin's method (*J.*, 1902, 280). Both samples dissolved in sulphuric acid to a greenish-yellow solution with a strong blue fluorescence.

The dibenzacridine gave a *picrate*, which crystallised from 2-ethoxyethanol in yellow needles, m. p. 326° (decomp.) (Found : C, 62·2; H, 3·3; N, 11·15. $C_{21}H_{13}N,C_6H_3O_7N_3$ requires C, 62·8; H, 3·2; N, 11·2%); the methosulphate, prepared by the method described by Kermack, Slater, and Spragg (*Proc. Roy. Soc. Edinburgh*, 1930, **50**, 258), crystallised from 95% alcohol in yellow needles, m. p. 308° (decomp.) (Found : N, 3·7. Calc. for $C_{21}H_{13}N,C_{13}H_8O_4S$: N, 3·5%) (Kermack *et al.*, *loc. cit.*, give m. p. >300°).

The ethereal filtrate from the trituration of the product, on treatment with light petroleum, gave 2-naphthylamine (3 g., 20%), identified by m. p. and mixed m. p.

N-2-*Cyanoethyl*-p-*anisidine*.—A mixture of *p*-methoxyanilinium benzenesulphonate (14 g.) (Partridge, *J.*, 1949, 2686) and 2-diethylaminoethyl cyanide (9·5 g., 1·5 mols.) was heated under reflux at 180° for 1 hour. Treatment of the cooled melt with acetone gave diethylammonium benzenesulphonate (9·0 g., 78·5%), m. p. and mixed m. p. 138—139°. The acetone filtrate on distillation afforded three fractions : (1) b. p. 41—42°/0·05 mm., unchanged 2-diethylaminoethyl cyanide (1·8 g., 0·22 mol.), n_D^{19} 1·4407; (2) b. p. 45—55°/0·05 mm., *p*-anisidine (1·4 g., 21%), as an oil, n_D^{19} 1·5450, solidifying to white crystals, m. p. 52—56° undepressed on admixture with an authentic specimen; (3) b. p. 170—180°/0·05 mm., white needles (6·0 g., 69%) of *N*-2-cyanoethyl-*p*-anisidine, m. p. 56—60°. Crystallisation from chloroform–light petroleum (b. p. 60—90°) afforded white nacreous plates, m. p. 63·5—64·5° (Found : N, 15·5. Calc. for $C_{10}H_{12}ON_2$: N, 15·9%). This compound is described by Elderfield *et al.* (*loc. cit.*) as a liquid, b. p. 247°/0·7 mm.

Diphenylammonium Benzenesulphonate.—This *salt* crystallised from alcohol–ether in white prisms, m. p. 124°, which became pink on exposure to light and air (Found : C, 65·6; H, 5·35; S, 10·15, 10·25. $C_{18}H_{17}O_3NS$ requires C, 66·05; H, 5·2; S, 9·8%).

Attempted Preparation of N-2-*Cyanoethyldiphenylamine*.—(*a*) Addition of diphenylammonium benzenesulphonate (13 g.) to 2-diethylaminoethyl cyanide (10 g., 2 mols.) gave an exothermic reaction, and a homogeneous melt was obtained immediately. The mixture was heated under reflux at 180° for 0·5 hour, cooled, and triturated with acetone, giving white needles (7·8 g., 85%) of diethylammonium benzenesulphonate, m. p. and mixed m. p. 139°. The acetone filtrate on distillation gave two fractions : (1) b. p. 120°/25 mm., recovered 2-diethylaminoethyl cyanide (3 g.); (2) b. p. 95—100°/0·05 mm., m. p. 54°, diphenylamine (mixed m. p.) (4·1 g., 61%). The residue from the distillation gave more diphenylamine (0·5 g., 7%).

(*b*) The same experiment was repeated at 200° for 1 hour. Trituration with acetone gave diethylammonium benzenesulphonate (6·7 g., 73·5%), m. p. and mixed m. p. 137—139°. Distillation of the acetone filtrate gave only two fractions : (1) b. p. 40—45°/0·05 mm., 2-diethylaminoethyl cyanide (5 g., 1 mol.); (2) b. p. 94—100°/0·05 mm., m. p. 52—54°, diphenylamine (5·3 g., 79%).

The authors thank Mr. E. Ritchie for helpful discussion, and Mrs. E. Bielski for microanalyses.

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732. *The Addition of Toluene-ω-thiol to Unsaturated Compounds.*

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The addition of toluene-ω-thiol to a series of unsaturated compounds is described. Addition products have in most cases been obtained in good yield, though toluene-ω-thiol is not as vigorous an additive agent as thiolacetic acid.

Some observations are made on the mechanism of the additions. Two addition reactions of methanethiol have also been included.

ADDITION reactions of toluene-ω-thiol have been the subject of considerable study in recent years. Nicolet (*J. Amer. Chem. Soc.*, 1935, **57**, 1098) showed that toluene-ω-thiol and benzylideneacetophenone gave β-benzylthio-β-phenylpropiophenone, and the addition of the thiol to various unsaturated hydrocarbons is described in the patent literature (Fife, B.P. 532,676). Several workers have reported the addition of toluene-ω-thiol to αβ-unsaturated acids, esters, aldehydes, ketones, and nitriles (Bougault and Chabrier, *Compt. rend.*, 1947, **224**, 395; Hurd and Gershbein, *J. Amer. Chem. Soc.*, 1947, **69**, 2328; Owen and Somade, *J.*, 1947, 1030; Catch, Cook, Graham, and Heilbron, *J.*, 1947, 1609; Süs, *Annalen*, 1948, **559**, 92; Földi and Kollonitsch, *J.*, 1948, 1683; Szabo and Stiller, *J. Amer. Chem. Soc.*, 1948, **70**,

3667; Banerjee, Chakraborty, and Dutta, *Sci. and Culture*, 1949, **14**, 438). In some cases peroxides were used as catalysts, and in others bases were found to be effective.

The investigations here described, carried out in 1945, deal with the addition of toluene-ω-thiol to some unsaturated compounds, in the presence of added peroxide. Generally, addition occurred readily and reasonable yields were obtained, but the thiol is not as vigorous an additive agent as thiolacetic acid (Brown, Jones, and Pinder, *J.*, 1951, 2123). In some cases the structure of the adduct has been proved, and in others the most probable structure has been assigned, in the light of previous experience.

$CH_2R{\cdot}S{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$ (I) $\quad$ $CH_2Ph{\cdot}S{\cdot}CHPh{\cdot}CH_2{\cdot}CO_2H$ (II) $\quad$ $CH_2Ph{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ (III)

The addition of toluene-ω-thiol to crotonic acid furnished β-(benzylthio)butyric acid (I; R = Ph). A comparison of the amide of the product with the amide of the isomeric α-(benzylthio)butyric acid, synthesised from α-bromobutyric acid, showed that the two compounds were different. Similarly, addition of methanethiol to crotonic acid gave β-(methylthio)butyric acid (I; R = H), the structure of which was proved in a similar manner by comparison with α-(methylthio)butyric acid. By analogy it was concluded that the product obtained by addition of toluene-ω-thiol to cinnamic acid was β-benzylthio-β-phenylpropionic acid (II).

The reaction of toluene-ω-thiol with *cyclo*hexene and styrene (Fife, *loc. cit.*) furnished adducts which were characterised as their crystalline sulphones. The peroxide-catalysed addition of toluene-ω-thiol to crotonaldehyde gave β-(benzylthio)butaldehyde, identical with the product obtained by Catch, Cook, Graham, and Heilbron (*loc. cit.*), by using piperidine as catalyst.

Szabo and Stiller (*loc. cit.*) have reported recently that the addition of toluene-ω-thiol to allyl alcohol gives 2-benzylthiopropanol, " Triton B " being used as catalyst. These authors did not characterise their product. We have found that in the presence of benzoyl peroxide, toluene-ω-thiol reacts with allyl alcohol to give 3-benzylthiopropanol (III) in good yield. The product was characterised as the *p*-nitrobenzoate and as the sulphone, both of which were obtained in almost quantitative yield. Efforts to separate these products into isomers by fractional crystallisation failed, and it is concluded that they were homogeneous. The sulphone proved to be identical in all respects with 3-benzylsulphonylpropanol, a specimen of which was prepared by condensation of toluene-ω-thiol and trimethylene chlorohydrin, followed by oxidation, as described by Rothstein (*J.*, 1934, 684).

These observations prompted us to repeat Szabo and Stiller's experiment, using " Triton B " as catalyst, in dioxan solution. We have found that the product is 3-benzylthiopropanol, and not 2-benzylthiopropanol, as stated by these authors. The yield of adduct was slightly better with " Triton B " as catalyst, than when benzoyl peroxide was employed.

$CH_2Ph{\cdot}S{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}OAc$ (IV) $\quad$ $CH_2Ph{\cdot}S{\cdot}CHPh{\cdot}CH_2{\cdot}CH_2{\cdot}OR$ (V)

By analogy with the mode of addition to allyl alcohol, the products obtained by the addition of toluene-ω-thiol to 2-methylallyl acetate, cinnamyl alcohol, and cinnamyl acetate are considered to be 3-benzylthio-2-methylpropyl acetate (IV), 3-benzylthio-3-phenylpropanol (V; R = H) and 3-benzylthio-3-phenylpropyl acetate (V; R = Ac), respectively.

Discussion.—If the yield of adduct may be regarded as a measure of the ease with which thiols add to double bonds, it is clear that toluene-ω-thiol is not as effective an additive agent as thiolacetic acid. The greater acidic strength of the latter may account partly for this difference, for Cunneen (*J.*, 1947, 36, 134) has shown that there is a parallelism between acidic strength of thiols and their ease of addition to olefinic bonds.

The production of the same adduct from toluene-ω-thiol and crotonaldehyde, in the presence of a base (Catch, Cook, Graham, and Heilbron, *loc. cit.*) or of a peroxide, is in harmony with the observations of Kharasch and Fuchs (*J. Org. Chem.*, 1948, **13**, 97), who have shown that thiols may add to methyl acrylate by either an ionic or a free-radical mechanism, both mechanisms resulting in the attachment of the sulphur atom to the β-carbon atom.

$CH_2{=}CH{\rightarrow}CH_2{\cdot}OH$ (VIII) $\quad$ $\overset{\oplus}{C}H_2{-}\dot{C}H{-}CH_2{\cdot}OH$ (IX)

The production of what is apparently the same homogeneous adduct from toluene-ω-thiol and allyl alcohol, in the presence of either base or peroxide, is rather surprising. This may be accounted for satisfactorily by a free-radical mechanism such as that proposed by Kharasch,

Read, and Mayo (*Chem. and Ind.*, 1938, **16**, 752). If, however, an ionic mechanism is involved, it becomes necessary to assume that the CH_2·OH group in allyl alcohol is sufficiently electrophilic ($+I$) to generate an electromeric change as in (VIII), giving a mesomeric state (IX). The thiol anion then adds at $C_{(3)}$ the product being 3-benzylthiopropanol.

Experimental.

β-(Benzylthio)butyric Acid.—Toluene-ω-thiol (31 g.), crotonic acid (21·5 g.), and ascaridole (5 drops) were heated under reflux on the water-bath for 3 hours. Fractional distillation of the product gave *β-(benzylthio)butyric acid* (50 g., 95%), b. p. 159—160°/1 mm. (Found: S, 15·4%; equiv., 208. $C_{11}H_{14}O_2S$ requires S, 15·2%; equiv. 210). The *amide*, prepared *via* the chloride, separated from ethyl alcohol in needles, m. p. 84—85° (Found: C, 62·9; H, 7·2; N, 6·8; S, 15·4. $C_{11}H_{15}ONS$ requires C, 63·2; H, 7·2; N, 6·7; S, 15·3%).

α-(Benzylthio)butyric Acid.—Toluene-ω-thiol (12·4 g.) was added to a cooled alcoholic solution of sodium ethoxide [from sodium (4·6 g.) in absolute alcohol (100 c.c.)]. The solution was cooled and stirred during the addition of α-bromobutyric acid (16·7 g.). After being heated under reflux on the water-bath for 2 hours, the mixture was cooled and filtered, and the filtrate evaporated to dryness *in vacuo*. The white residue was dissolved in water (100 c.c.), and the solution acidified with hydrochloric acid. *α-(Benzylthio)butyric acid*, isolated with ether, distilled at 150—152°/1 mm. (15 g.) (Found: S, 15·2%; equiv., 208·8). The *amide*, obtained in the usual manner, crystallised from water in fine needles, m. p. 106—107° (Found: C, 63·2; H, 7·2; N, 6·7; S, 15·3. $C_{11}H_{15}ONS$ requires C, 63·2; H, 7·2; N, 6·7; S, 15·3%). A mixture of this amide and *β*-(benzylthio)butyramide (see above) had m. p. 75—76°.

β-(Methylthio)butyric Acid.—Crotonic acid (21·5 g.), methanethiol (12·0 g.; prepared as described by Phillips and Clarke, *J. Amer. Chem. Soc.*, 1923, **45**, 1756), and a trace of ascaridole were heated in an autoclave at 80° for 3 hours. Fractional distillation of the product gave *β-(methylthio)butyric acid* (60%), b. p. 98—100°/1 mm. (Found: S, 23·05%; equiv., 131·6. $C_5H_{10}O_2S$ requires S, 23·9%; equiv., 134). The *amide* separated from light petroleum (b. p. 60—80°) in plates, m. p. 79—80° (Found: C, 45·4; H, 8·5. $C_5H_{11}ONS$ requires C, 45·1; H, 8·3%).

α-(Methylthio)butyric Acid.—An alcoholic solution of sodium ethoxide [from the metal (4·6 g.) in absolute alcohol (150 c.c.)] was stirred and cooled to 0° during the addition of methanethiol (4·3 g.), followed by α-bromobutyric acid (16·7 g.). After being heated under reflux on the water-bath for 2 hours, the mixture was cooled and filtered, and the filtrate evaporated to dryness. The white residue was dissolved in water (100 c.c.) and acidified with hydrochloric acid. α-(Methylthio)butyric acid, isolated with ether, distilled at 90—91°/1 mm. (80%) (Found: S, 23·8%; equiv., 132). Mooradian, Cavallito, Bergman, Lawson, and Suter (*J. Amer. Chem. Soc.*, 1949, **71**, 3372) give b. p. 115—116°/8 mm. The *amide* separated from light petroleum (b. p. 60—80°) in short needles, m. p. 98—99° (Found: C, 44·8; H, 8·4; N, 10·4. $C_5H_{11}ONS$ requires C, 45·1; H, 8·3; N, 10·5%). A mixture of this amide and *β*-(methylthio)butyramide (see above) had m. p. 68—70°.

β-Benzylthio-β-phenylpropionic Acid.—Cinnamic acid (30 g.), toluene-ω-thiol (75 g.), and ascaridole (5 drops) were heated under reflux on the water-bath for 8 hours. When the mixture cooled, unreacted cinnamic acid separated and was collected, and unchanged toluene-ω-thiol was removed *in vacuo*. The gummy residue gradually solidified; *β-benzylthio-β-phenylpropionic acid* separated from light petroleum (b. p. 60—80°) in needles, m. p. 80—81° (35%) (Found: C, 71·0; H, 6·6%; equiv., 270. $C_{16}H_{16}O_2S$ requires C, 70·6; H, 5·9%; equiv., 272).

*Benzylthio*cyclo*hexane.*—A mixture of *cyclo*hexene (30 g.), toluene-ω-thiol (60 g.), and ascaridole (5 drops) was heated under reflux on the water-bath for 8 hours. Fractional distillation gave benzylthio*cyclo*hexane, b. p. 126°/3 mm. (40%) (Found: S, 15·8. Calc. for $C_{13}H_{18}S$: S, 15·5%) (cf. Fife, *loc. cit.*). Oxidation of the product (2·0 g.) in glacial acetic acid (15 c.c.) with perhydrol (4·5 g.) furnished *benzyl* cyclo*hexyl sulphone* (1·9 g.), which separated from ethyl alcohol in glistening needles, m. p. 101—102° (Found: S, 13·5. $C_{13}H_{18}O_2S$ requires S, 13·4%).

Benzyl 2-Phenylethyl Sulphide.—Styrene (30 g.), toluene-ω-thiol (40 g.), and ascaridole (5 drops) were heated under reflux on the water-bath for 4½ hours. Fractional distillation gave the *sulphide* (93%), b. p. 154—158°/3 mm. (Found: S, 14·3. Calc. for $C_{15}H_{16}S$: S, 14·0%) (cf. Fife, *loc. cit.*). Oxidation of the product (3·0 g.) in glacial acetic acid (15 c.c.) with perhydrol (7·5 g.) gave *benzyl 2-phenylethyl sulphone* (3·0 g.), needles, m. p. 125—126°, from ethyl alcohol (Found: S, 12·7. $C_{15}H_{16}O_2S$ requires S, 12·3%).

β-Benzylthiobutaldehyde.—Crotonaldehyde (14 g.), toluene-ω-thiol (24·8 g.), and ascaridole (5 drops) were refluxed on the water-bath for 3 hours. Fractional distillation gave *β*-benzylthiobutaldehyde (70%), b. p. 120—123°/2 mm. (Found: S, 16·6. Calc. for $C_{11}H_{14}OS$: S, 16·5%). The 2 : 4-dinitrophenylhydrazone separated from ether–light petroleum (b. p. 60—80°) in orange needles, m. p. 68° (Found: C, 54·3; H, 4·6; N, 15·0. Calc. for $C_{17}H_{18}O_4N_4S$: C, 54·5; H, 4·8; N, 15·0%). Catch, Cook, Graham, and Heilbron (*loc. cit.*) give m. p. 69°.

β-Methylthiobutaldehyde.—Crotonaldehyde (19·5 g.), methanethiol (12 g.), and ascaridole (5 drops) were heated in an autoclave at 80° for 3 hours. Fractionation of the product *in vacuo* gave *β-methylthiobutaldehyde* (67%), b. p. 40°/2·5 mm. (Found: S, 27·6. $C_5H_{10}OS$ requires S, 27·1%). The 2 : 4-*dinitrophenylhydrazone* separated from methyl alcohol in orange plates, m. p. 85—86° (Found: C, 44·4; H, 5·4; N, 19·1. $C_{11}H_{14}O_4N_4S$ requires C, 44·3; H, 4·7; N, 18·8%).

3-*Benzylthiopropanol.*—Allyl alcohol (11·6 g.), toluene-ω-thiol (24·8 g.), and benzoyl peroxide (few mg.) were heated under reflux on the water-bath for 24 hours, and then boiled under reflux for a

further 20 hours. Fractional distillation of the product furnished 3-benzylthiopropanol (51%), b. p. 156—158°/5 mm. (Found: S, 17·8. Calc. for $C_{10}H_{14}OS$: S, 17·6%). Oxidation of the product with perhydrol furnished 3-benzylsulphonylpropanol, clusters of glistening needles, m. p. 126—127°, from benzene (Found: C, 56·3; H, 6·2. Calc. for $C_{10}H_{14}O_3S$: C, 56·1; H, 6·5%). The *p-nitrobenzoate* crystallised from methyl alcohol in pale cream prisms, m. p. 49—50° (Found: C, 61·7; H, 5·2. $C_{17}H_{17}O_4NS$ requires C, 61·6; H, 5·1%). These derivatives proved to be identical in all respects with the corresponding derivatives of a specimen of 3-benzylthiopropanol prepared by Rothstein's unambiguous method (*loc. cit.*).

A repetition of Szabo and Stiller's experiment (*loc. cit.*) gave 3-benzylthiopropanol (70%) exclusively, identical in all respects with the above product, and not the 2-isomer, as reported by these authors.

3-Benzylthio-3-phenylpropanol.—Cinnamyl alcohol (40 g.), toluene-ω-thiol (40 g.), and ascaridole (5 drops) were refluxed on the water-bath for 8 hours. Fractional distillation gave *3-benzylthio-3-phenylpropanol* (47%), b. p. 175°/3 mm. (Found: S, 12·9. $C_{16}H_{18}OS$ requires S, 12·4%).

3-Benzylthio-2-methylpropyl Acetate.—A similar experiment with 2-methylallyl acetate (35 g.), toluene-ω-thiol (40 g.), and ascaridole (5 drops) gave *3-benzylthio-2-methylpropyl acetate* (73%), b. p. 130°/1 mm. (Found: S, 13·8. $C_{13}H_{18}O_2S$ requires S, 13·4).

3-Benzylthio-3-phenylpropyl Acetate.—From cinnamyl acetate (35 g.), toluene-ω-thiol (35 g.), and ascaridole (5 drops), refluxed on the water-bath for 8 hours, was obtained *3-benzylthio-3-phenylpropyl acetate* (38%), b. p. 184—186°/3 mm. (Found: S, 10·5. $C_{18}H_{20}O_2S$ requires S, 10·7%).

The authors thank Miss D. E. Lofthouse for assistance, and the Chief Scientist, Ministry of Supply, for permission to publish this paper.

RESEARCH ESTABLISHMENT,
SUTTON OAK, ST. HELENS, LANCS. [*Received, August 16th*, 1951.]

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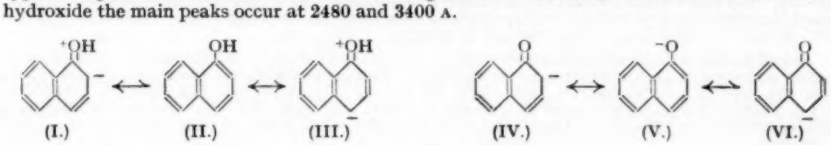
733. *Ultra-violet Absorption Spectra of Some Derivatives of Quinoline, Quinazoline, and Cinnoline.*

By (MISS) J. M. HEARN, R. A. MORTON, and J. C. E. SIMPSON.

The absorption spectra of 4-hydroxy-, 4-hydroxy-6-nitro-, and 4-amino-quinolines have been compared with those of related compounds of fixed structure. Similar investigations have been made on quinazoline and cinnoline derivatives. The absorption curves show that, when alternative formulations are possible, quinolone, quinazolone, and cinnolone structures are either predominant or at least important.

THE absorption spectrum of α-naphthol (Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68** 2181) is a convenient starting point for the present work. The structures (I) and (III) in resonance with (II), which involve separation of charges, contribute little to absorption in neutral solution. In alkaline solutions the corresponding quinonoid forms (IV) and (VI) contribute strongly to the resonance and account for the bathochromic effect in passing from neutral to alkaline solution. Thus, in 95% ethanol $\lambda_{max.}$ occurs at 2350 A. and 2800 A. with typical naphthalenic narrow bands in the region 3000—3250 A., whereas in 0·01N-sodium hydroxide the main peaks occur at 2480 and 3400 A.



(I.) (II.) (III.) (IV.) (V.) (VI.)

In solutions of quinoline the non-polar structures are more important than the polar structures, again because of separation of charges, but the quinolinium ion formed on acidification, with its positive charge, makes probable a number of resonance forms accounting for a bathochromic displacement. Thus, in 95% ethanol $\lambda_{max.}$ is at 2780 ($\varepsilon_{max.}$ 3500), whereas in 0·01N-hydrochloric acid $\lambda_{max.}$ occurs at 3150 A. ($\varepsilon_{max.}$ 7000). In alkaline solution there is little change as compared with neutral solution.

A similar shift occurs with *iso*quinoline and 5-hydroxy*iso*quinoline, except that alkali, too, effects a change in the spectrum of the latter.

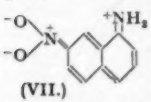
In 8-hydroxyquinoline the spectrum of the neutral solution is displaced in both 0·1N-hydrochloric acid and 0·01N-sodium hydroxide, whereas the curves for 8-methoxyquinoline agree with those of the parent substance except that there is no bathochromic effect in an alkaline

medium. There appears to be no hydrogen bridging, since the 8-hydroxy- and 8-methoxy-compounds do not differ in neutral or acid solutions.

On the other hand, 1-hydroxy*iso*quinoline (1-*iso*quinolone) shows practically the same absorption spectrum in ethanol, dilute acid, or alkali and resembles 2-methyl-1-*iso*quinolone so closely as to fix the structure (of the parent substance) as *iso*quinolone. The absence of bathochromic effects leads to the broad conclusion that " those quinoline and *iso*quinoline derivatives which have the hydroxyl substituted in the pyridine ring in the α- or γ-positions relative to the nitrogen may be written as ketonic compounds " (Ewing and Steck, *loc. cit.*).

The quinolone structure for 2-hydroxyquinoline (carbostyril) was already established by comparison of the spectra of the parent substance with those of the *O*-methyl ether and the *N*-methyl ether (Morton and Rogers, *J.*, 1925, **127**, 2698; Ault, Hirst, and Morton, *J.*, 1935, 653).

Mononitronaphthylamines, *e.g.*, 1-amino-7-nitronaphthalene (VII) (pK_a 2·93), exhibit quinonoid contributions (Hodgson and Hathway, *Trans. Faraday Soc.*, 1945, **41**, 115; 1947, **43**, 643; Bryson, *ibid.*, 1949, **45**, 257).



(VII.)

The possibility that 4-aminoquinoline may exist as the imino-form has been clearly recognized, but decisive evidence to show that it does in fact so exist under ordinary conditions has not yet been obtained (cf. Albert and Goldacre, *Nature*, 1944, **153**, 167; Irvin and Irvin, *J. Amer. Chem. Soc.*, 1947, **69**, 1091; Steck and Ewing, *ibid.*, 1948, **70**, 3397). The case of 5-aminoacridine, which might offer an analogy, is also unsettled (Albert and Ritchie, *J.*, 1943, 458; Craig and Short, *J.*, 1945, 419; Wilkinson and Finar, *J.*, 1946, 115).

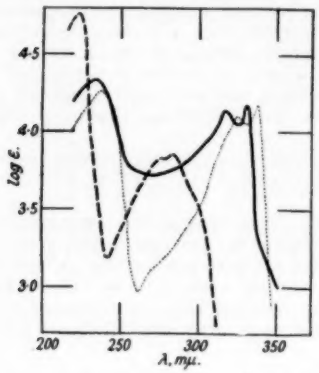
TABLE I.

Quinoline derivatives. $\lambda_{max.}$ (A.) *and* log $\varepsilon_{max.}$

4-Hydroxyquinoline	3315	3175	2335					3260	2720		
	4·18	4·15	4·35					4·06	3·74		
1-Methyl-4-quinolone	3380	3250	2370					3310	2605		
	4·18	4·11	4·27					4·06	2·97		
4-Methoxyquinoline	~2950	2830	2755	2255				2415			
	3·60	3·86	3·83	4·78				3·18			
4-Hydroxy-6-nitro-quinoline	3500	~3220	2650					2900	2455		
	3·87	3·81	4·10					3·4	3·86		
1-Methyl-6-nitro-4-quinolone	3580	3260	2660					3445	2920	2495	
	3·92	3·94	4·12					3·89	3·41	3·93	
4-Methoxy-6-nitro-quinoline	3430	2990	2660					3230	2780		
	3·64	3·90	4·37					3·52	3·75		
6-Nitro-4-phenoxy-quinoline	3415	2960	2570					3220	2815	2330	
	3·65	3·94	4·36					3·54	3·80	4·12	
4-Hydroxyquinoline-3-carboxylic acid	~3215	3100	~3005	~2530	2410			2665	2355		
	3·95	4·07	4·02	4·27	4·36			3·38	4·34		
4-Hydroxy-6-methoxy-quinoline-3-carb-oxylic acid	~3450	~3260	3100	~2900	2590	2500	2380	2760	2560	2425	
	3·63	3·86	3·92	3·80	4·33	4·39	4·38	3·66	4·28	4·32	
4-Aminoquinoline	3200	2330						2660			
	4·01	4·28						2·98			
5-Aminoquinoline	3550	2520						2890			
	3·48	4·42						2·95			
6-Aminoquinoline	3575	2880	2460					3130	2745		
	3·58	3·59	4·56					3·09	3·57		
4-Acetamidoquinoline	3135	2985	2265					2585			
	3·85	3·98	4·65					3·40			
4-Anilinoquinoline	3360	2440						2790	2335		
	4·16	4·34						3·29	4·29		
4-Amino-6-nitroquinoline	3920	3240	2790					3460	3085	2450	
	3·75	3·65	4·36					3·38	3·59	3·85	
4-Acetamido-6-nitro-quinoline	3535	3055	2640	2255				3295	2860	2400	
	3·64	3·94	4·27	4·40				3·53	3·80	4·05	
4-Anilino-6-nitro-quinoline	3980	3355	2835	2500				3540	3135	2690	2420
	3·94	3·73	4·26	4·35				3·58	3·63	4·18	4·32
4-Chloro-6-nitroquinoline	2940	2530						2740			
	3·91	4·62						3·78			

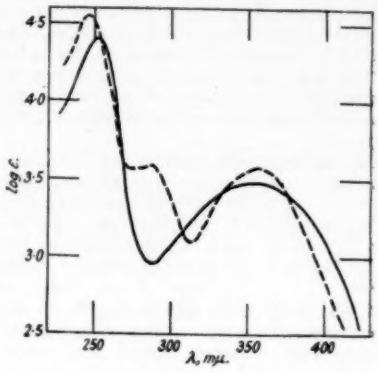
A series of investigations (Simpson *et al.*, *J.*, 1942, 353; 1943, 447; 1945, 512, 520; 1946, 480, 1035; 1947, 227, 232, 237; 1948, 354, 358, 360, 1170, 1702, 1707) has made available a range of compounds suitable for spectrophotometric study. We wish to associate with these

FIG. 1.



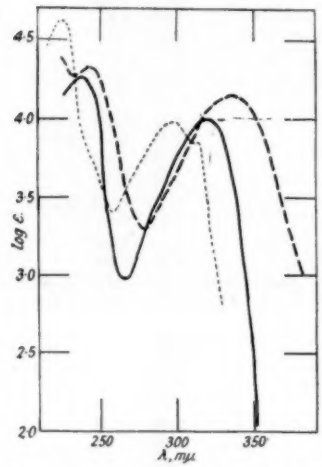
Absorption curves for: ——— *4-hydroxyquinoline,* – – – – *4-methoxyquinoline,* . . . . *1-methyl-4-quinolone.*

FIG. 2.



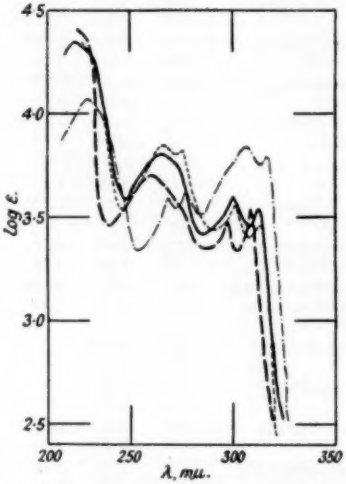
Absorption curves for: ——— *5-aminoquinoline,* – – – – *6-aminoquinoline.*

FIG. 3.



Absorption curves for: ——— *4-aminoquinoline,* ——— ——— *4-anilinoquinoline,* – – – – *4-acetamidoquinoline.*

FIG. 4.



Absorption curves for: ——— *4-hydroxyquinazoline,* ——·——·—— *1-methyl-4-quinazolone,* – – – – *3-methyl-4-quinazolone,* ——— ——— *4-methoxyquinazoline.*

studies the names of our colleagues, Drs. C. M. Atkinson, J. S. Morley, and K. Schofield, Mr. J. R. Keneford, and Mr. P. H. Wright, to whom our best thanks are due for the preparation of the majority of the samples used in this work.

Quinoline Derivatives.—Table I summarises the data for quinoline derivatives. Fig. 1 shows that the spectrum of 4-hydroxyquinoline resembles that of 1-methyl-4-quinolone very

closely and is very different from that of 4-methoxyquinoline. The relatively high absorption between 2500 and 3000 A. would, however, be consistent with some contribution from the hydroxy-form, although the quinolone structure is evidently the important one.

Similarly (see Table I) 4-hydroxy-6-nitroquinoline, with its absorption strikingly similar to that of 1-methyl-6-nitro-4-quinolone and quite dissimilar from that of 4-methoxy-6-nitro- (or 6-nitro-4-phenoxy)-quinoline, is clearly a quinolone.

Introduction of a carboxyl group to give 4-hydroxyquinoline-3-carboxylic acid results in a rather small bathochromic shift as compared with 4-methoxyquinoline, but from the spectra it seems probable that the carboxyl group in position 3 inhibits the formation of a quinolone. Introduction of a methoxy-group in position 6 displaces the spectrum without apparently changing its character.

In the aminoquinolines, the 5- and 6-amino-compounds, with $\lambda_{max.}$ about 3550 A. (log $\varepsilon_{max.}$ *ca.* 3·5), are very different from 4-aminoquinoline (Figs. 2 and 3). The spectrum of the latter resembles that of 4-hydroxyquinoline which, as already stated, is essentially quinolone in structure, and it therefore follows that an imino-structure must be ascribed to 4-aminoquinoline. 4-Anilinoquinoline gives a spectrum like that of 4-aminoquinoline but slightly displaced in the direction of longer wave-lengths and is probably "quinolone" in structure; 4-amino- and 4-anilino-6-nitroquinoline are very different in spectra from 4-chloro-6-nitroquinoline, the latter being clearly a quinoline in structure. On the other hand, although the argument from analogy is not infallible, it seems likely that 4-acetamido- and 4-acetamido-6-nitro-quinoline resemble in spectra 4-methoxy- and 4-methoxy-6-nitro-quinoline closely enough to exclude quinonoid structures.

TABLE II.

Quinazoline derivatives. $\lambda_{min.}$ (A.) *and* log $\varepsilon_{min.}$

4-Hydroxyquinazoline	3130	3005	2650	2235		3080	2860	2480	
	3·54	3·60	3·81	4·36		3·45	3·41	3·59	
1-Methyl-4-quinazolone	3170	3065	2775	2690	2300	3140	2850	2725	2545
	3·79	3·84	3·63	3·60	4·08	3·76	3·52	3·55	3·34
3-Methyl-4-quinazolone	3135	3015	2760	2670	2300	3080	2910	2730	2475
	3·46	3·56	3·82	3·85	4·35	3·40	3·44	3·81	3·54
4-Methoxyquinazoline	3090	2975	2610	2250		3030	2870	2395	
	3·54	3·48	3·71	4·42		3·34	3·35	3·46	
4-Phenoxyquinazoline	3100	2980	2635			3040	2900	2430	
	3·62	3·57	3·79			3·54	3·50	3·72	
4-Hydroxy-6-nitroquinazoline	3165					2700			
	4·01					3·38			
1-Methyl-6-nitro-4-quinazolone	3220					2740			
	4·02					3·56			
3-Methyl-6-nitro-4-quinazolone	3175	2226				2710			
	4·14	4·41				3·35			
4-Methoxy-6-nitroquinazoline	~3250	2950				2545			
	3·64	3·91				3·59			
6-Nitro-4-phenoxyquinazoline	2985					2685			
	3·94					3·73			
4-Aminoquinazoline	~3290	3245	3130	2840	~2400	2990	2540		
	3·60	3·67	3·83	3·86	4·14	3·71	3·51		
4-Acetamidoquinazoline	3140	2810	2430			2970	2646	2380	
	3·86	3·82	4·15			3·63	3·73	4·10	
4-Anilinoquinazoline	3330	2940	2345			3025	2690	2285	
	4·19	3·90	4·16			3·88	3·75	4·13	
4-Amino-6-nitroquinazoline	3320	2550				2850	2430		
	3·92	4·24				3·38	4·15		
4-Acetamido-6-nitroquinazoline	3310	2520				2840	2410		
	3·92	4·17				3·61	4·06		
4-Anilino-6-nitroquinazoline	3640	2395				3025			
	4·04	4·41				3·60			

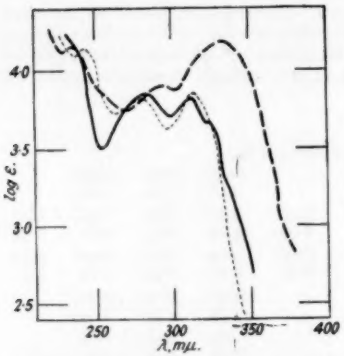
Quinazoline Derivatives.—The absorption curve for quinazoline shows maxima near 3100 (log ε 3·3) and 2700 A. (log ε 3·35) with very intense absorption (log ε 4·5) near 2200. The spectra of a number of substituted compounds are recorded in Table II. The curve for 4-methoxyquinazoline (Fig. 4) shows sharp maxima near 3090 and 2975 A. (log ε *ca.* 3·5) and

2610 A. (log ε 3·71). Now among the possible structures for 4-hydroxyquinazoline are (VIII)—(X). From the spectra of the methyl-substituted derivatives of fixed structure the following approximate molecular extinction coefficients would be expected (Fig. 4).

λ (A.):	*ca.* 3100	3000	2760	2650	2610	2300
(VIII)	3430	3000	—	—	5100	26000
(IX)	6200	6900	4200	4000	—	12000
(X)	2900	3600	6700	7000	—	22000
Observed	3460	3980	—	6460	—	22800

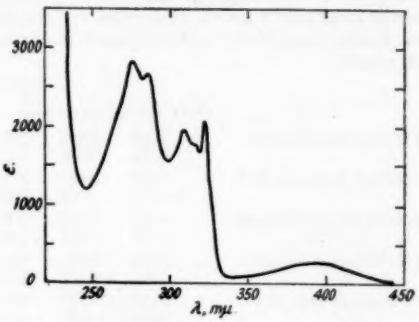
Since the observed ε value at 3000 A. is greater than that at 3100, (VIII) cannot be the exclusive structure. It is equally clear that neither (IX) nor (X) can be the sole structure. Is, therefore, (VIII) in equilibrium with (IX) or (X) or both? The ε values for (X) are clearly too low to account for the rise near 3000 A. which requires some of (IX). In the region 2600—2650 A. the evidence points, on the other hand, to (VIII) and (X) being in equilibrium. The intensities at 2300 A. would fit with a small amount of (VIII) being present, but would not

FIG. 5.



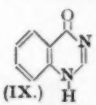
Absorption curves for: ——— *4-aminoquinazoline*, – – – – *4-acetamidoquinazoline*, —— —— —— *4-anilinoquinazoline*.

FIG. 6.

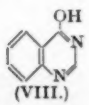


Absorption curve for cinnoline (*in* cyclo*hexane*).

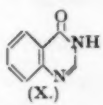
exclude both (IX) and (X) being present. So far as the argument goes all three structures are possible and indeed probable.



(IX.)



(VIII.)



(X.)

By taking the intensities of the two long-wave peaks and solving simultaneous equations, structures (VIII), (IX), and (X) appear to be present to the extent of 17·8, 14·4, and 67·8%, respectively. By taking the peaks near 2230 and 2700 A. the corresponding figures are 23, 4, and 73%. Careful inspection of the curves shows that the curve for 4-hydroxyquinazoline could be accounted for if it were (X) to the extent of 70 ± 2·5% and (IX) 10 ± 5% and (VIII) 20 ± 2·5%.

The whole argument may however be weakened by second-order effects of methylation on ε values.

The corresponding 6-nitroquinazoline derivatives quite strongly favour a structure for 4-hydroxy-6-nitroquinazoline resembling that of 3-methyl-6-nitro-4-quinazolone with very little of the quinazoline alternative. 4-Phenoxyquinazoline shows a spectrum very closely similar to that of the 4-methoxy-compound.

In the case of 4-aminoquinazoline the data indicate a quinazoline rather than a quinazolone structure. Thus, 4-acetamidoquinazoline differs little from the 4-amino-compound (Fig. 5).

4-Amino-6-nitroquinazoline shows a spectrum much closer to that of the 4-methoxy-6-nitroquinazoline than that of the two quinazolones.

Cinnoline Derivatives.—The absorption curve of cinnoline (Fig. 6) does not appear to have been obtained before. There is first a weak maximum at 3900 A. (ε 265) which may well owe its origin to the presence of the $-N{=}N-$ group in the molecule. The three maxima at 3085, 3170, and 3225 A. (ε values 1960, 1770, and 2080, respectively) seem to belong to one band system and are reminiscent of naphthalene. The two maxima at 2755 and 2860 A. are more intense (ε 2820 and 2650, respectively) and there is intense absorption below 2300 A. The curve was obtained in *cyclo*hexane.

TABLE III.

Cinnoline derivatives. $\lambda_{min.}$ (A.) *and* log $\varepsilon_{min.}$.

4-Hydroxycinnoline	3520	3430	3380	2960	2845	2620	3490	3010	2905	2740	2600
	4·09	4·10	4·14	3·43	3·44	3·85	4·01	3·31	3·36	3·32	3·84
	2550	2370					2460				
	3·95	4·05					3·87				
1-Methyl-4-cinnolone	3690	3520	2515				3590	2890	2390		
	4·11	4·11	3·95				4·00	3·05	3·80		
4-Methoxycinnoline	3130	2910	2240				3040	2580			
	3·65	3·74	4·57				3·55	3·26			
4-Phenoxycinnoline (in *cyclo*hexane)	3230	~3200	3105	2925	2825	2250	3160	3040	2860	2535	
	3·69	3·66	3·64	3·82	3·80	4·68	3·59	3·56	3·79	3·33	
4-Ethoxycinnoline (in *cyclo*hexane)	3625	3215	3180	3100	2905	2800	3420	3195	3160	3025	2850
	2·67	3·57	3·42	3·43	3·79	3·79	3·55	3·40	3·40	3·37	3·77
≈3930, 3900, 3830, 3770							2810				
							3·24				
4-Hydroxy-6-nitrocinnoline	3645	3245	2670	2360			3350	2910	2560		
	4·09	3·94	3·97	4·16			3·85	3·40	3·94		
1-Methyl-6-nitro-4-cinnolone	3700	3280	2695	2410			3400	2940	2625		
	4·11	3·97	3·91	4·22			3·80	3·37	3·89		
4-Methoxy-6-nitrocinnoline	3535	3000	2905	~2550	2430		3130	2960	2820		
	3·73	3·68	3·74	4·19	4·28		3·26	3·66	3·64		
6-Nitro-4-phenoxycinnoline	3535	2895	2540				3150	2815	2495		
	3·76	3·79	4·08				3·39	3·75	4·05		
4-Hydroxy-3-methylcinnoline	3585	3475	2920	2810	2500	2375	3530	3025	2875	2730	2470
	4·03	4·06	3·52	3·52	3·97	4·08	3·97	3·09	3·40	3·31	3·93
3-Ethyl-4-hydroxycinnoline	3575	3440	2915	2825	2495	2375	3525	3015	2820	2715	2470
	4·06	4·07	3·62	3·59	4·01	4·12	4·01	3·18	3·50	3·40	3·98
4-Hydroxy-6 : 7-dimethylcinnoline	3620	3470	2895				3580	3060	2820		
	3·91	3·99	3·40				3·89	3·25	3·32		
4-Hydroxy-3-methyl-6-nitrocinnoline	3760	3255	~2700	2385			3400	2890			
	4·21	4·04	3·97	4·32			3·90	3·45			
4-Hydroxycinnoline-3-carboxylic acid	~3540	~3460	3390	2630	~2380		2850	2530			
	3·97	4·04	4·10	3·87	4·05		3·28	3·69			
4-Hydroxy-6-methoxycinnoline-3-carboxylic acid	3520	2545					2870	2420			
	4·08	4·30					3·22	4·20			
4-Hydroxy-6 : 7-methylenedioxycinnoline	3580	3485	3410	2925	2650	2565	3525	3455	2980	2810	2610
	4·19	4·10	4·16	3·43	4·22	4·25	4·08	4·07	3·42	3·36	4·13
	2450	2370					2510	2410			
	4·22	4·20					4·19	4·20			
3-Chloro-4-hydroxy-6-methylcinnoline	3515	2990	2880	2435			3090	2955	2765		
	4·07	3·66	3·63	4·16			3·28	3·52	3·44		
6-Bromo-3-chloro-4-hydroxycinnoline	3675	3510	3030	2910	2495		3595	3140	2965	2735	2260
	4·04	4·01	3·87	3·78	4·31		3·96	3·40	3·04	3·29	3·86
3 : 6-Dibromo-4-hydroxycinnoline	3690	3500	3040	2910	2530		3610	3140	2990	2730	2265
	4·05	4·01	3·94	3·82	4·31		3·97	3·42	3·70	3·30	3·89
Methyl 4 : 6 : 7-trimethoxy-3-cinnolylacetate	3640	3510	2940	2700	2620	2345	3560	3025	2880	2650	2530
	4·14	4·14	3·43	4·35	4·31	4·39	4·09	3·32	3·42	4·27	4·13
Methyl 6 : 7-dimethoxy-1-methyl-3-cinnolon-4-ylacetate	3790	3630	2810	2730	2405		3700	2965	2770	2610	
	4·18	4·14	4·15	4·16	4·58		4·08	3·26	4·13	4·00	
Tetrahydro-4 : 6-diketocinnoline 6-oxime methyl ether *N*-oxide	3990	3355	3220	~2800	2585	~2360	3440	3280	3100	2310	
	4·11	3·60	3·49	3·82	4·20	3·94	3·45	3·51	3·30	3·86	

TABLE III.—(*continued*).

4-Acetoxy-3-chloro-6-methylcinnoline	3515 4·05	2645 4·18	2470 4·32			3050 3·23	2590 4·12		
4-Acetoxy-3-chloro-6 : 7-dimethylcinnoline	3490 4·09	3075 3·59	2675 4·22	2460 4·34		3135 3·56	2930 3·50	2610 4·19	2300 4·00
4-Acetoxy-6-nitrocinnoline	3620 3·96	3235 4·05	2630 4·10	2360 4·20		3400 3·88	2910 3·57	2540 4·04	
4-Acetoxy-6-chlorocinnoline	3465 4·12	3000 3·55	2460 4·33			3050 3·48	2940 3·53		
4-Aminocinnoline	3450 4·06	2400 4·10				2750 2·99			
4-Acetamidocinnoline	3285 3·87	3035 3·90	~2510 3·64	2260 4·63		3135 3·80	2695 3·39		
4-Anilinocinnoline	3640 4·18	2480 4·16				2900 3·30	2360 3·99		
4-Amino-6-nitrocinnoline	4020 3·91	3265 3·72	2720 4·17	2552 4·20		3495 3·46	3010 3·43	2635 4·11	2425 4·04
4-Acetamido-6-nitrocinnoline	3620 3·86	3050 3·86	2600 4·23	2290 4·7		3245 3·48	2870 3·7	2550 4·18	
4-Anilino-6-nitrocinnoline	4180 4·07	3435 3·79	2780 4·07	2470 4·39		3610 3·60	3160 3·60	2730 4·05	

4-Ethoxycinnoline has been examined in detail in *cyclo*hexane solution (Fig. 7). There is first a region of low absorption with a maximum near 3625 A. and inflexions at 3770, 3830, 3900, and 3930 A. indicative of vibrational structure (with perhaps a frequency difference of about 450 cm.$^{-1}$). There is next a group of three maxima of moderate intensity, $\lambda_{max.}$ 3100, 3180, and 3215 A.; these bands clearly have their counterparts in the cinnoline spectrum but the ϵ values are appreciably raised as a result of substitution. The next group consists of two peaks at 2800 and 2905 A. which are increased in intensity about two-fold compared with the corresponding peaks in the cinnoline curve. As in cinnoline, there is a deep minimum near 2500 A. and the curve rises sharply, indicating very intense absorption beyond 2300 A. 4-Methoxy- and 4-phenoxy-cinnoline in ethanol and in *cyclo*hexane are essentially similar except that solubilities do not always allow quite so full a set of measurements. This type of substitution does not seriously affect the positions of maxima on the wave-length scale, but the probabilities of the relevant electronic transitions are all increased by the substitution.

1-Methyl-4-cinnolone (Fig. 8) shows twin maxima at 3520 and 3690 A. with a marked inflexion near 3300 A. (Δ cm.$^{-1}$ 1309). There is a very low minimum at 2890 A. and a new maximum near 2515 A.

4-Hydroxycinnoline shows maxima at 3380 (~3430) and 3520 A. (Δ cm.$^{-1}$ *ca.* 1200). These bands clearly correspond with the long-wave bands of 1-methyl-4-cinnolone. Two maxima at 2845 and 2965 A. quite clearly correspond with the 2800 and 2905 A. maxima of 4-ethoxycinnoline and the 2910 A. band of 4-methoxycinnoline. 4-Ethoxycinnoline has a minimum at 2510 A. and 1-methyl-4-cinnolone has a maximum at 2515 A. 4-Hydroxycinnoline also shows a maximum near 2550 A. of low persistence.

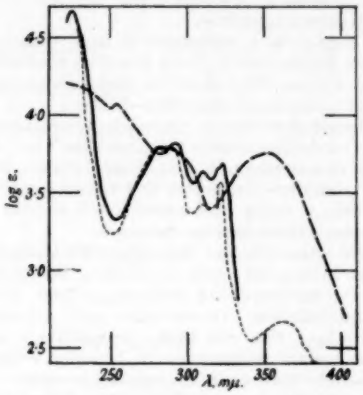
It is clear that 4-hydroxycinnoline in ethanol is in equilibrium with its tautomer, but it is not possible, from the information available, to calculate the proportions precisely. The displacement of the curve of 4-hydroxycinnoline which appears in 1-methyl-4-cinnolone (3380—3520 A.; 3520—3690 A.) is not negligible and the basis of calculating the proportions of isomerides from absorption intensities at 2900 A. is to assume that the minimum for the cinnolone tautomer of 4-hydroxycinnoline agrees in position with that of the homologous 1-methyl-4-cinnolone. However, there may well be 30% of 4-hydroxycinnoline. As judged from the regions near 3500 and 2500 A., the cinnolone tautomer obviously preponderates. The intensity of absorption of this entity would need to be greater than that of 1-methyl-4-cinnolone to make the spectra completely consistent.

Substitution of methyl groups in 4-hydroxycinnoline in positions 3, 6, and 7 makes practically no difference in the spectrum which remains consistent with some 70% of cinnolone and 30% of cinnoline. The same applies to introduction of an ethyl group in position 3. The compound 4-hydroxy-6 : 7-methylenedioxycinnoline is preponderately of cinnolone type.

A specially simple spectrum is shown by 4-hydroxycinnoline-3-carboxylic acid. The 3380, 3430, and 3520 A. selective absorption of 4-hydroxycinnoline is shown practically un-

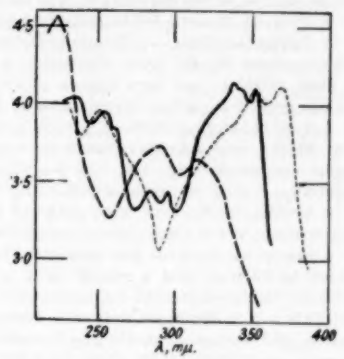
changed and there is a deep minimum near 2850 A. and a maximum near 2630 A. The carboxylic acid is unequivocally a cinnolone. The same applies to 4-hydroxy-6-methoxycinnoline-3-carboxylic acid.

FIG. 7.



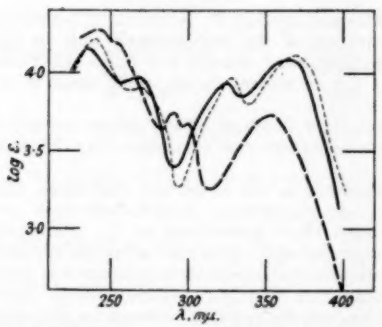
Absorption curves for: ——— *4-phenoxycinnoline,* – – – – *4-ethoxycinnoline,* —— —— —— *6-nitro-4-phenoxycinnoline.*

FIG. 8.



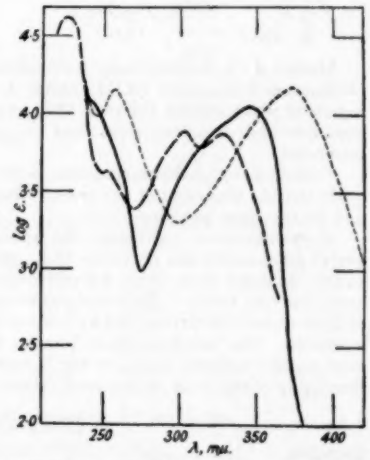
Absorption curves for: ——— *4-hydroxycinnoline,* —— —— —— *4-methoxycinnoline,* – – – – *1-methyl-4-cinnolone.*

FIG. 9.



Absorption curves for: ——— *4-hydroxy-6-nitrocinnoline,* —— —— —— *4-methoxy-6-nitrocinnoline,* – – – – *1-methyl-6-nitro-4-cinnolone.*

FIG. 10.



Absorption curves for: ——— *4-aminocinnoline,* —— —— *4-acetamidocinnoline,* – – – – *4-anilinocinnoline.*

Inspection of the curves of the halogen-substituted cinnolines 3-chloro-4-hydroxy-6-methylcinnoline, 6-bromo-3-chloro-4-hydroxycinnoline, and 3 : 6-dibromo-4-hydroxycinnoline suggests the co-existence of cinnolines and cinnolones in equilibrium. The minimum near 2900 A. has disappeared and the two strong bands of the cinnoline structure are clearly seen.

An interesting extension of the argument is seen in the spectra of the 6-nitro-derivatives (Fig. 9).

1-Methyl-6-nitro-4-cinnolone agrees very closely with 4-hydroxy-6-nitrocinnoline, which must therefore be a cinnolone. The *N*-methyl compound shows only a small bathochromic

shift. The 2900 A. minimum persists. Introduction of a nitro-group displaces the part of the absorption curve on the long-wave side of about 3400 A.

Similarly, the spectrum of 4-methoxy-6-nitrocinnoline closely resembles that of 4-methoxycinnoline except that the nitro-group brings about a bathochromic shift which is least for the middle section of the curve from 2750 to 3000 A. and greatest for the region near 3500 A.

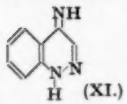
4-Hydroxy-3-methyl-6-nitrocinnoline is evidently also a cinnolone.

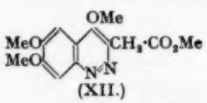
4-Aminocinnolines.—4-Ethoxycinnoline being accepted as a compound of fixed structure, the cinnolines should have absorption in the region 3100—3300 A., with selective absorption at 2800—2900 A. and very intense absorption near 2260 A. The cinnolone structure shows a peak near 3500 A., a deep minimum near 2900 A., and a maximum near 2500—2550 A.

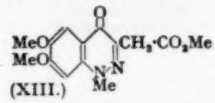
4-Aminocinnoline shows $\lambda_{max.}$ 3450 A. with an inflexion near 3250 A.; there is a deep minimum near 2750 A. and a further maximum near 2400 A.; it is thus clearly a "cinnolone," *i.e.*, the imino-compound (Fig. 10). In 4-anilinocinnoline the situation is not wholly clear. Provisionally, it may be taken as possessing the same "cinnolone" structure as 4-aminocinnoline.

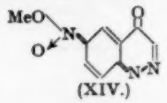
4-Acetamidocinnoline, with peaks at 3285 and 3035 A. and a very intense band at 2260 A., clearly resembles 4-alkoxycinnolines and does not possess the cinnolone structure.

4-Acetamido-6-nitro- and 4-acetamido-3-methyl-6-nitro-cinnoline show the 3285 band displaced to 3620 A., and a second peak near 3000 A. corresponds with the 3035 A. maximum. 4-Diacetylamino-3-methyl-6-nitrocinnoline is of fixed structure and with $\lambda_{max.}$ 3500, 2830, and 2220 A.; it compares well with 4-methoxy-6-nitrocinnoline. On the other hand, 4-amino-6-nitro- and 4-amino-3-methyl-6-nitro-cinnoline, with $\lambda_{max.}$ 4000 and 4085 A., respectively, and maxima near 3250, 2750, 2550, and 2270 A., show a clear resemblance to 1-methyl-6-nitro-4-cinnolone. It therefore seems legitimate to conclude that 4-aminocinnoline possesses the structure (XI) but that substitution in the amino-group results in the cinnoline type of structure.


(XI.)


(XII.)


(XIII.)


(XIV.)

Methyl 4 : 6 : 7-trimethoxy-3-cinnolylacetate (XII) and methyl 6 : 7-dimethoxy-1-methyl-(4-cinnolon-3-yl)acetate (XIII) afford a clear illustration of the bathochromic shift in the region of wave-lengths between 3500 and 4000 A. without much change in ε values when the cinnoline and cinnolone structures are compared. The structures shown would seem to be confirmed.

Tetrahydro-4 : 6-diketocinnoline 6-(oxime methyl ether *N*-oxide) (XIV) raises questions quite outside the scope of our present discussion because its structure is substantially different and its spectrum puzzling.

Acetylcinnolines. Although the spectroscopic evidence is not absolutely conclusive, the acetyl compounds are probably *O*-Ac rather than *N*-Ac derivatives. Acetyl derivatives are easily obtained from most 4-hydroxycinnolines except those substituted at $C_{(8)}$ (Keneford *et al.*, *loc. cit.*, 1950). These compounds have been regarded as *O*-acetyl derivatives on account of their ease of formation and hydrolysis, but no conclusive evidence of their structure has been available. The spectrographic data for the compound from 4-hydroxy-6-nitrocinnoline, however, clearly indicate that it is the *N*-acetyl derivative, and the possibility cannot be excluded that other compounds of this group should be similarly formulated.

TABLE IV. $\lambda_{max.}$ (A.) *and* $\varepsilon_{max.}$.

Quinoline	λ 3140	3000	2780	[2350]		
	ε 3000	2600	3500	35000		
*iso*Quinoline	λ 3200	3080	2600, 2670, 2708			
	ε 2700	2500	3700			
Quinazoline		λ 3080	2700	2200		
				4·6		
		ε 3000	3200	*ca.* 40000		
Cinnoline	λ 3900	3225	3170	3085	2860	2760
	ε 265	2080	1770	1960	2650	2820

Comparisons of Spectra of Analogous Compounds of Different Heterocyclic Series.—Table IV shows that the spectra of quinoline, *iso*quinoline, quinazoline, and cinnoline, in ethanol, are fundamentally similar in that substitution of N for CH does not completely change the character

of the curves. In cinnoline, however, there is some contribution from the ·N=N· grouping, giving rise to low-intensity long-wave-length selective absorption. Table V compares quinolone, quinazolone, and cinnolone derivatives, and Table VI gives relevant information on quinoline, *iso*quinoline, and 5- and 8-quinolinols (Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181).

TABLE V. $\lambda_{max.}$ (A.) *and* $\varepsilon_{max.}$

1-Methylquinolone	λ 3380	3250	2370		
	ε 15200	12800	18700		
1-Methyl-4-quinazolone	λ 3170	3065	2775	2690	2300
	ε 6220	6890	4220	3940	12100
3-Methyl-4-quinazolone	λ 3135	3015	2764	2670	2300
	ε 2880	3620	6680	7030	22400
1-Methyl-4-cinnolone	λ 3690	3520	2515		
	ε 12900	12700	8900		

TABLE VI. $\lambda_{max.}$ (A.) *and* $\varepsilon_{max.}$

Quinoline :	in 95% EtOH	λ 3140 sharp		3000	2780	2250
		ε 3000		2600	3500	35000
	in 0·01N-HCl	λ 3150			2350	
		ε 7000			35000	
*iso*Quinoline :	in 95% EtOH	λ 3200	3080	2600	2670	2780
		ε 2700	2500		3700	
	in 0·01N-NaOH	similar to spectrum in 95% EtOH				
	in 0·01N-HCl	λ 3350	2670	2730	2300	
		ε 4000		*ca.* 2000	40000	
5-Quinolinol :	in 95% EtOH	λ 3280		2400		
		ε 3000		37300		
	in 0·1N-HCl	λ 3700	3150	3050	2520	
		ε 2500	1700		40000	
	in 0·1N-NaOH	λ 3670	3306		2540	
		ε 3500	2800		30000	
8-Quinolinol :	in 95% EtOH	λ 3100			2400	
		ε 3200			50000	
	in 0·01N-HCl	λ 3580	3200—3080		2500	
		ε 1950	1800		48000	
	in 0·01N-NaOH	λ 3500			2550	
		ε 3000			32000	

8-Quinolinyl methyl ether curves agree very closely except that there is no shift in alkali.

TABLE VII. $\lambda_{max.}$ (A.) *and* $\varepsilon_{max.}$

4-Hydroxyquinoline	λ 3315	3175			2335		
	ε 15200	14100			22300		
4-Hydroxyquinazoline	λ 3130	3005	2650		2235		
	ε 3460	3980	6460		22800		
4-Hydroxycinnoline	λ 3520	3380	2960	2845	2620	2550	2570
	ε 12200	13800	2700	2770	7050	8910	11200

All the above compounds exist in solution in equilibrium with ketonic forms.

4-Methoxyquinoline	λ ~3100	~2950	2830	~2755	2255	
	ε 4000	3980	7280	7760	60000	
4-Methoxyquinazoline	λ 3090	2975		2610	2250	
	ε 3430	3000		5110	26000	
4-Methoxycinnoline	λ 3130	2910			2240	
	ε 4500	5500			37500	

The spectrum of 3-methyl-4-quinazolone shows a notable resemblance to those of quinoline and *iso*quinoline, whilst 1-methyl-4-quinazolone has a spectrum similar to that of quinoline in 0·01N-acid. In 1-methylquinolone there is a decided wave-length shift and the ε values are much increased. The shift is still greater in 1-methylcinnolone but the twin bands persist. All the 4-methoxy-derivatives (Table VII) illustrate the relatively small changes in band intensities resulting from substitution which leaves the respective rings practically unchanged.

Introduction of nitro-groups (Table VIII) displaces all the spectra in the direction of longer wave-lengths but in no case is there evidence of fundamental molecular rearrangement as a result. The 4-amino-derivatives of quinoline (-one), quinazoline (-ine), and cinnoline (-one) (Table IX) maintain the broad similarity seen throughout the series, but the intensity of absorption for the quinazoline is lower than that of the quinolone and the cinnolone.

TABLE VIII. $\lambda_{max.}$ (A.) *and* $\varepsilon_{max.}$

4-Methoxy-6-nitroquinoline	λ	3430	2990	2660	
	ε	4390	7960	23600	
4-Methoxy-6-nitroquinazoline	λ	3250	2950		
	ε	4390	8180		
4-Methoxy-6-nitrocinnoline	λ	3530	3000	2905	2430
	ε	5370	4790	5520	19100

Introduction of the nitro-groups displaces the spectra in the direction of longer wave-lengths but exerts no fundamentally new effect.

1-Methyl-6-nitro-4-quinolone	λ	3580	3260	2660	
	ε	8360	8710	13200	
1-Methyl-6-nitro-4-quinazolone	λ	3220	2740		
	ε	10500	3650		
3-Methyl-6-nitro-4-quinazolone	λ	3175		2220	
	ε	13800		25400	
1-Methyl-6-nitro-4-cinnolone	λ	3700	3280	2695	2410
	ε	12900	9330	8040	16700

The effect of the nitro-group is here variable both on values and on positions of maxima.

TABLE IX. $\lambda_{max.}$ (A.) *and* $\varepsilon_{max.}$

4-Aminoquinoline (-one)	λ	3200		2330	
	ε	10200		19000	
4-Aminoquinazoline (-ine)	λ	3245	3130	2846	~2400
	ε	4700	6730	7180	13700
4-Aminocinnoline (-one)	λ	3450	~3250	2400	
	ε	11500	*c.* 9000	12606	

Correlations between Chemical and Spectrographic Properties.—Although the chemical and spectrographic properties of a compound reflect different activated states, yet a number of interesting correlations are discernible for the compounds under discussion between the spectral data given above and some of their known chemical properties (Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356; 1950, 1104).

(i) There is significant agreement between the fine structures of 4-hydroxy-compounds of each type, as deduced from spectral evidence, and the constitutions of the methylated derivatives which these compounds yield on treatment with methyl sulphate and alkali. Thus 4-hydroxycinnoline, -quinazoline, and -quinoline are all mainly keto-dihydro in structure, and each gives rise to an *N*-methyl derivative. Furthermore, spectrographic data show that the mobile hydrogen in 4-hydroxy- and 4-hydroxy-6-nitro-quinazoline is attached mainly to $N_{(3)}$, and each compound gives the 3-methyl derivative as the sole product isolated.

(ii) Chemical evidence indicates that 4-hydroxycinnolines contain a more mobile replaceable hydrogen atom than do their quinazoline or quinoline counterparts (Keneford *et al.*, *loc. cit.*, 1950). This greater chemical reactivity may be connected with the fact that the " hydroxy-aromatic " form makes a larger contribution in the hydroxy-cinnolines than in the other two series; for whereas the " keto-dihydro " form is present almost exclusively in 4-hydroxyquinoline, yet the quinazoline analogue contains about 20%, and most 4-hydroxycinnolines about 30%, of the " hydroxy-aromatic " tautomer.

(iii) Of the various simple compounds in each series that have been examined both spectrographically and chemically, the hydroxy- and amino-compounds are the only ones for which two or more fine structures differing tautomerically are possible. For the hydroxy-compounds and other 4-substituted derivatives it has been shown that the quinoline compound is more basic than the quinazoline analogue, which in turn is more basic than the corresponding cinnoline derivative; for 4-amino-compounds, however, the order of basic strength is quinoline > cinnoline > quinazoline (Keneford *et al.*, *loc. cit.*, 1949). Although no fundamental explanation of the deviation here seen in the amino-series could be advanced, the results suggested that

either 4-aminocinnoline or 4-aminoquinazoline (but not both) differed significantly in fine structure from the other two amino-analogues. The spectrographic evidence now obtained shows quite clearly that this is indeed the case, because it requires the ascription of imino-structures to 4-aminoquinoline and 4-aminocinnoline, and an amino-structure to 4-amino-quinazoline.

It is of interest that, among the three types of 4-amino-compound, only the amino-quinazolines are hydrolysed in acid solution (Keneford *et al.*, *loc. cit.*, 1950); but, as the participating entity is here the ion and not the free base, the reaction cannot be correlated directly with the spectrographic data.

(iv) Quinazoline shows a greater spectrographic resemblance to 3-methyl-4-quinazolone than it does to the 1-methyl isomer. This may be held to correspond with the observed quaternisation of quinazoline at $N_{(3)}$ (Gabriel and Colman, 1904).

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734. *Spectrophotometric Determinations of the Second Dissociation Constant (as pK_a) of 5- and of 6-Aminoquinoline.*

By (MISS) J. M. HEARN, R. A. MORTON, and J. C. E. SIMPSON.

The absorption spectra at different pH values being used, pK_a values for 5- and 6-aminoquinoline are found to be about 0·97 and 1·63, respectively, for the mono-cation–di-cation change, as against 5·5 and 5·6 for the first pK_a values (due to acceptance of a proton by the ring nitrogen atom) previously determined potentiometrically.

THE absorption curves of 5- and 6-aminoquinoline vary markedly with the pH of the medium. The spectra of both substances dissolved in 2N-hydrochloric acid bear an unmistakable resemblance to that of quinoline in 0·01N-hydrochloric acid, *i.e.*, to that of the quinolinium ion. A similar resemblance between the spectra of benzene and of aniline in hydrochloric acid is well known (cf. Scheibe, Backenkoller, and Rosenberg, *Ber.*, 1926, **59**, 2617; Harberts, Heertjes, Hulst, and Waterman, *Bull. Soc. chim.*, 1936, **3**, 643; Sklar, *J. Chem. Physics*, 1939, **7**, 984; *Rev. Mod. Physics*, 1942, **14**, 232; Kumler and Stra[illegible] *J. Amer. Chem. Soc.*, 1943, **65**, 2349). The same resemblance is shown between 3-, 8-, and 10-amino-1 : 2-benzanthracene in hydrochloric acid and 1 : 2-benzanthracene; between 5-amino-3 : 4-benzopyrene in acid and 3 : 4-benzopyrene; and between 4-aminopyrene in hydrochloric acid and pyrene (Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127). Furthermore, the spectra of the heterocyclic compounds, pyridine, quinoline, and acridine resemble respectively those of benzene, naphthalene, and anthracene (Braude, *Ann. Reports*, 1945, **42**, 105).

Craig and Short (*J.*, 1945, 419) have observed that for all monoaminoacridines except the 5-isomeride the absorption spectra in 5N-hydrochloric acid agree with that shown by acridine itself in acid (acridinium ion). The amino-group in 5-aminoacridine is not converted at any time into the NH_3^+ form. By showing that the spectrum of the acridinium ion is observable only at low pH values when the di-cations of the aminoacridines are formed and not at an intermediary pH value (*e.g.*, 3), Craig and Short proved that the ring nitrogen atom accepts the first proton on acidification, and the nitrogen atom of the amino-group accepts the second. The former atom is thus the more basic one.

As shown below, the ring nitrogen atom in 5- and 6-aminoquinoline also accepts the first proton and the absorption spectrum shows a bathochromic shift. The second proton is accepted by the amino-nitrogen atom and the spectrum is changed to that of the quinolinium ion.

If the absorption spectra are determined quantitatively at various accurately determined pH values, pK_a values for the change from mono-cation to di-cation can be obtained. The equation

$$pK_a = pH - \log[(\varepsilon_{BH^+} - \varepsilon)/(\varepsilon - \varepsilon_B)]$$

TABLE I.

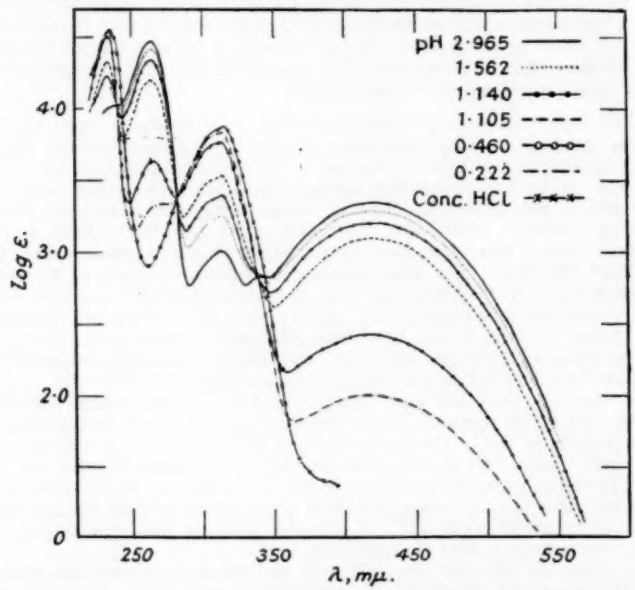
Absorption maxima and minima in quinoline and 5- and 6-aminoquinoline.

		$\lambda_{max.}$, A.				$\lambda_{min.}$, A.		
Quinoline :								
in 95% EtOH *	λ 3120	2980	2780		3100	2950	2430	
	ε 3000	2800	3500		1900	2700	1500	
in 0·01N-HCl	λ 3120	2350			2500			
	ε 6900	35000			190			
5-Aminoquinoline :								
in abs. EtOH	λ 3550	2520			2890			
	ε 3000	26000			900			
in *ca.* 0·005N-NaOH (aq. EtOH)	λ 3420	2480			2815	225		
	ε 3090	28200			944	9550		
in *ca.* 0·01N-HCl	λ 4240	3140	2630	2340	3355	2905	2380	
	ε 2100	1100	30000	10000	600	680	9000	
in *ca.* 2N-HCl	λ 3150	2670	2340		2715	2500		
	ε 6610	2140	34300		1950	1200		
6-Aminoquinoline :								
in EtOH	λ 3575	2880	2460		3130	2745		
	ε 3780	3910	36310		1220	3750		
in *ca.* 0·01N-HCl	λ 3820	3085	2590		3330	2920	2360	
	ε 3240	2940	27500		1170	2390	8650	
in *ca.* 0·005N-NaOH (aq. EtOH)	λ 3460	2825	2430		3055	2735	2210	
	ε 3670	3410	34000		1330	3160	16000	

* Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.

FIG. 1.

Absorption spectra of 5-aminoquinoline in aqueous hydrochloric acid.



(Irvin and Irvin, *J. Amer. Chem. Soc.*, 1946, **68**, 2181) applies to measurements of molecular extinction coefficients (ε) at a given wave-length; ε_{BH^+} is determined at a low pH value at which the equilibrium is overwhelmingly in favour of the proton-donor BH^+, and ε_B at some higher pH value at which the solute exists almost entirely as the proton-acceptor B; ε is the molecular extinction coefficient at a defined or measured intermediate pH at which B and BH^+ co-exist.

TABLE II.

ε Values for 5-aminoquinoline at various pH *values* (see Fig. 1).

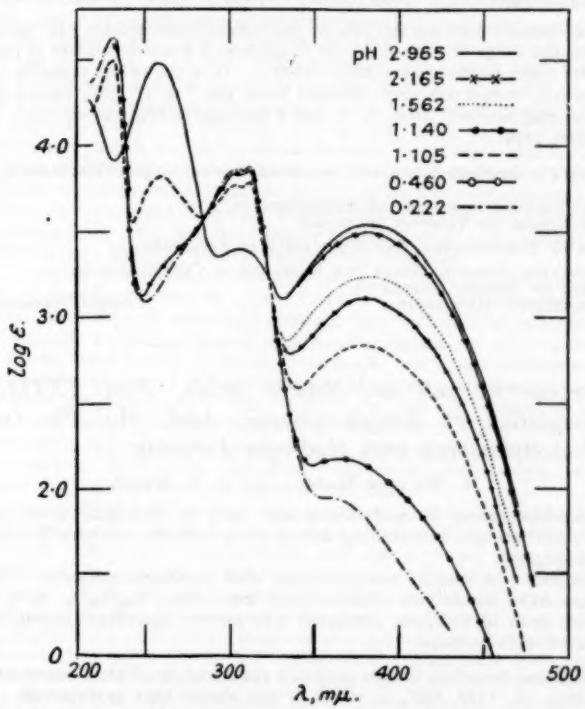
pH:	2·965	2·165	1·562	1·140	1·105	0·460	0·222	Conc. HCl
$\lambda_{max.}$, A.								
4160—4200	2210	2140	1940	1600	1260	270	100	0·24
3400	680	670	—	—	—	—	—	—
3120—3140	1030	1170	1790	2520	3440	5930	6900	7620
2700	—	—	—	—	—	—	2160	—
2640	29800	28500	26400	22100	15900	4330	—	—
2330—2350	10400	10400	14200	16900	21300	32800	35400	36200

Not all wave-lengths will be equally suitable; at some points near to isosbestic points the values of $\Delta\varepsilon/\Delta\lambda$ may be high for the different ions and the results may be inaccurate. The validity of the procedure depends, however, on the existence of such crossing points in the spectra.

Table I shows that the change from ethanol to 0·01N-acid results in displacement of spectra, whereas alkali causes a shift in the opposite direction. Between 0·01N-acid and 2N-acid the spectra acquire the characteristics of the quinolinium ion (quinoline in 0·01N-acid).

FIG. 2.

Absorption spectra of 6-aminoquinoline in aqueous hydrochloric acid.



The data in Tables II and III were obtained by using a Beckman spectrophotometer, and the pH readings were made with a Marconi pH meter.

For both 5- and 6-aminoquinoline the mono-cations exist alone at pH 2·965 and the di-cations exist alone in concentrated hydrochloric acid.

TABLE III.

ε *Values for 6-aminoquinoline at various* pH *values* (see Fig. 2).

pH:	2·965	2·165 *	1·562 *	1·14 *	1·105	0·460	0·222
$\lambda_{max.}$ A.:							
3820	3520	3190	1720	1300	688	—	—
3650—3700	—	—	—	—	—	151	—
~3620	—	—	—	—	—	—	87·6
3120	—	—	—	—	6130	7200	7550
3050	2510	—	—	—	6900	6900	7200
2600	—	—	—	—	6630	—	—
2580	30300	—	—	—	—	—	—
2320	—	—	—	—	31200	39500	42600

* Readings made from 3400 to 5000 A. only.

Calculations of pK_a values were carried out at a large number of wave-lengths for the different pH values between the extremes. For 5-aminoquinoline calculations were made at 60-A intervals between 3650 and 5700 A., and for 6-aminoquinoline at 100-A. intervals between 3400 and 4700 A. The results are shown below:

pK_a *Values.*

pH at which curve was measured ...	2·165	1·562	1·140	1·105	0·460	0·222	
5-Aminoquinoline (average)	0·628	0·698	0·707	1·037	1·314	1·456	Average 0·97
6-Aminoquinoline (average)	1·240	1·591	1·414	1·820	2·092	—	Average 1·63

The degree of agreement between the pK_a at the various intermediate pH values is resonably good considering the range and the fact that in neither of the two families of curves is there a *strictly* isosbestic point in the region 3300—3500 A. It is, however, perfectly clear that the overall average pK_a values are very different from the "first" pK_a values of 5·5 and 5·6 recorded for the ring nitrogen atom in 5- and 6-aminoquinoline, respectively, by Morley and Simpson (*J.*, 1949, 1014).

We are indebted to the Medical Research Council for financial support (Biochemistry Dept.).

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[*Received, February 22nd,* 1951.]

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735. *Triterpene Resinols and Related Acids. Part XXIII.** (a) *The Decarboxylation of Acetylketoursolic Acid.* (b) *The Oxidation of Methyl Acetylursolate with Hydrogen Peroxide.*

By WILLIAM MANSON and F. S. SPRING.

Decarboxylation of acetylketoursolic acid in quinoline gives nor-α-amyrenonyl acetate in which the ketone group and the ethylenic linkage are not conjugated.

Oxidation of methyl acetylursolate with hydrogen peroxide yields a mixture from which two stereoisomeric keto-esters, $C_{33}H_{52}O_6$, have been isolated, each of which is converted into methyl acetylketo*iso*ursolate on treatment with bromine.

(*a*) THE investigation described in this part is a continuation of that described in Part XIV (Ewen and Spring, *J.*, 1943, 523), in which it was shown that acetylursolic acid resembles α-amyrin acetate in yielding an αβ-unsaturated ketone on oxidation with chromic anhydride. The product, acetylketoursolic acid, resembled acetylketo-oleanolic acid in that when heated with quinoline it loses the elements of formic acid to give a conjugated dienone showing a high-intensity absorption maximum at approximately 3000 Å. These facts were interpreted as

* Part XXII, *J.*, 1951, 3019.

indicating that the carboxyl group of ursolic acid, like that of oleanolic acid, is in the neighbourhood of the ethylenic linkage. Although nor-α-amyradienonyl acetate, obtained from ursolic acid, and the nor-β-isomer, obtained from oleanolic acid (Ruzicka, Cohen, Furter, and Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735), both show absorption maxima at approximately 3000 Å, the molecular extinction coefficients of these maxima are markedly different, that of nor-β-amyradienonyl acetate being approximately 22,000 and that of nor-α-amyradienonyl acetate being 10,000. The decarboxylation of acetylketoursolic acid was therefore re-examined.

When heated in quinoline, the conditions described in Part XIV being used, acetylketoursolic acid gives a neutral product, m. p. 206—208°, $[\alpha]_D$ +45°, which in these respects is very similar to the nor-α-amyradienonyl acetate described by Ewen and Spring (m. p. 203—205°; $[\alpha]_D$ +41°). Like Ewen and Spring's nor-α-amyradienonyl acetate, the compound, m. p. 206—208°, showed an absorption maximum at approximately 3000 Å, the molecular extinction coefficient of which was, however, only 6000. The decarboxylation of acetylketoursolic acid in quinoline is accompanied by the formation of resinous material and in an attempt to avoid this, the reaction was carried out in a nitrogen atmosphere. In these conditions, the neutral reaction product gives a compound, $C_{31}H_{48}O_3$, m. p. 216—217°, $[\alpha]_D$ +37°, which gives a yellow coloration with tetranitromethane in chloroform and does not exhibit selective absorption in the ultra-violet. The presence in the compound, m. p. 216—217°, of one ethylenic linkage was established by its oxidation with perbenzoic acid to a monoxide, which gives no colour with the tetranitromethane reagent. The compound, $C_{31}H_{48}O_3$, is therefore a nor-α-amyrenonyl acetate produced by decarboxylation of acetylketoursolic acid with simultaneous migration of the ethylenic linkage. Hydrolysis of nor-α-amyrenonyl acetate gave nor-α-amyrenonol, m. p. 257—259°, $[\alpha]_D$ +34°, acetylation of which regenerated the parent acetate.

The properties of nor-α-amyrenonyl acetate, of Ewen and Spring's nor-α-amyradienonyl acetate, and of the compound, m. p. 206—208°, described above, apart from the selective light absorption, are very similar, and the possibility that the last two compounds are mixed crystals of nor-α-amyradienonyl acetate with variable proportions of nor-α-amyrenonyl acetate became apparent. A chromatographic examination of the compound, m. p. 206—208°, showing selective absorption at 3000 Å, $\varepsilon = 6000$, was undertaken in the hope that it would lead to a separation of nor-α-amyrenonyl acetate and nor-α-amyradienonyl acetate. This did not prove to be the case; nor-α-amyrenonyl acetate was readily isolated in relatively high yield from the least strongly adsorbed fractions of the chromatogram but subsequent fractions, which gave strong brown colorations with the tetranitromethane reagent and showed an absorption maximum at 2980 Å ($\varepsilon = 10{,}500$), could not be obtained crystalline.

The decarboxylation of triterpenoid keto-acids in the presence of quinoline does not appear to give uniformly reproducible results. Thus Ruzicka, Cohen, Further, and Sluys-Veer (*loc. cit.*) showed that treatment of acetylketo-oleanolic acid with boiling quinoline gave nor-β-amyradienonyl acetate, a result confirmed by Ewen and Spring (*loc. cit.*). Bilham, Kon, and Ross (*J.*, 1942, 535) were unable to repeat this result; using the conditions described by Ruzicka and his collaborators they obtained as sole product nor-β-amyrenonyl acetate, produced by decarboxylation and migration of the ethylenic linkage. Subsequently in a repetition of the original experiment, Ruzicka, Jeger, and Winter (*Helv. Chim. Acta*, 1943, **26**, 265) obtained a mixture of approximately equal amounts of nor-β-amyrenonyl acetate and nor-β-amyradienonyl acetate. In a recent repetition of this experiment using a purified quinoline we have obtained nor-β-amyrenonyl acetate as sole product.

(*b*) Oxidation of methyl acetylursolate with hydrogen peroxide gives a product, $C_{33}H_{52}O_5$, m. p. 250—253°, $[\alpha]_D$ +25°, which is either methyl acetylursolate oxide or methyl acetyldihydroketoursolate. Oxidation of acetylursolic acid with hydrogen peroxide gave a mixture of a neutral and an acidic product. The latter was not obtained crystalline but was esterified with diazomethane. Chromatographic purification of the ester fraction gave the compound, $C_{33}H_{52}O_5$, identical with that obtained by direct oxidation of methyl acetylursolate. The compound, $C_{33}H_{52}O_5$, m. p. 250—253°, is probably identical with the methyl acetyldihydroketoursolate described by Jeger, Borth, and Ruzicka (*Helv. Chim. Acta*, 1946, **29**, 1999). Since oxidation of α-amyrin esters with hydrogen peroxide yields the corresponding oxides, we at first inclined to the view that the compound, $C_{33}H_{52}O_5$, is methyl acetylursolate oxide. When treated with hydrochloric acid, the compound, $C_{33}H_{52}O_5$, gave an isomer, m. p. 254—256°, $[\alpha]_D$ +35°. In spite of the similarity in physical properties, the two compounds are distinct, a mixture showing a pronounced depression in melting point. There are substantial reasons for discarding the view that the isomers, m. p. 250—253° and m. p. 254—256°, are oxide and saturated ketone, respectively. Both exhibit low-intensity maxima in the region of 2900 Å,

indicating that each is a saturated ketone. α-Amyrin acetate oxide (+114°) and α-amyranonyl acetate (+11°) differ very considerably in their specific rotations, as do α-amyrin benzoate oxide (+132°) and α-amyranonyl benzoate (+25°), whereas the isomeric compounds, $C_{33}H_{52}O_4$, show no such striking difference in specific rotation. We conclude that the latter pair are stereoisomeric methyl acetyldihydroketoursolates.

The relationship between the isomeric keto-esters is further established by their behaviour on treatment with bromine in presence of hydrogen bromide when they each give the same αβ-unsaturated keto-ester, methyl acetylketo*iso*ursolate (Dreiding, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1325). Bromination of methyl acetyldihydroketoursolate under relatively mild conditions gave the intermediate methyl acetylbromodihydroketoursolate which when warmed with acetic acid loses hydrogen bromide, yielding methyl acetylketo-*iso*ursolate.

Experimental.

M.p.s are uncorrected; specific rotations were measured at room temperature (15—19°) in chloroform in a 10-cm. tube.

Acetylketoursolic Acid.—A boiling solution of acetylursolic acid (5 g.), m. p. 286—289°, $[\alpha]_D$ +62° (*c*, 1·3), in glacial acetic acid (125 c.c.) was oxidised with chromic anhydride, the conditions described by Ewen and Spring (*loc. cit.*) being used with the difference that the period of reflux was 2 hours. Acetylketoursolic acid (2·7 g.) was obtained as stout prismatic needles, m. p. 323—325° (decomp.), $[\alpha]_D$ +89° (*c*, 1·4) (the value +41° given by Ewen and Spring is incorrect) (Found: C, 74·9; H, 9·3. Calc. for $C_{32}H_{48}O_5$: C, 75·0; H, 9·4%). Light absorption in ethanol: Maximum at 2500 Å, ε = 12,500.

Ethyl acetylketoursolate separates from aqueous methanol as stout prismatic needles, m. p. 215—216°, $[\alpha]_D$ +85° (*c*, 1·0) (Found: C, 75·4; H, 9·5. Calc. for $C_{34}H_{52}O_5$: C, 75·6; H, 9·7%). Light absorption in ethanol: Maximum at 2500 Å, ε = 10,500.

Methyl acetylketoursolate was prepared by esterification of acetylketoursolic acid by use of diazomethane. It separates from aqueous ethanol as stout needles, m. p. 243—245°, $[\alpha]_D$ +86° (*c*, 0·91) (Found: C, 75·1; H, 9·8. $C_{33}H_{50}O_5$ requires C, 75·3; H, 9·5%). Light absorption in ethanol: Maximum at 2500 Å, ε = 10,500.

Nor-α-amyrenonyl Acetate.—A solution of acetylketoursolic acid (0·69 g.) in dry, freshly distilled quinoline (30 c.c.) was gently refluxed for 18 hours. Throughout the reaction, a slow stream of nitrogen was passed through the solution. The issuing gas stream was cooled at −10°, and passed through a standard solution of barium hydroxide. After 8 hours the carbon dioxide absorption corresponded to 0·3 mol. and after 16 hours to 0·8 mol. The cooled reaction mixture was poured into excess of dilute hydrochloric acid and extracted with ether. The extract was washed with dilute hydrochloric acid, water, and finally with dilute sodium hydroxide solution which precipitated an insoluble sodium salt (0·12 g.). The sodium salt was dissolved in hot aqueous ethanol, and the solution acidified (Congo-red) with dilute hydrochloric acid. On cooling, acetylketoursolic acid separated as prismatic needles, m. p. 310—313° undepressed when mixed with the starting material. After removal of the sodium salt, the ethereal solution was washed with water and dried (Na_2SO_4). Removal of the ether gave a crystalline solid (0·46 g.) after which four recrystallisations from aqueous ethanol gave *nor-α-amyrenonyl acetate* (0·30 g.) as plates, m. p. 216—217°, $[\alpha]_D$ +37° (*c*, 0·94), which gave a yellow coloration with tetranitromethane in chloroform (Found: C, 79·1; H, 10·2. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%).

Nor-α-amyrenonol.—Nor-α-amyrenonyl acetate (0·07 g.) was refluxed for 3 hours with ethanolic potassium hydroxide (5%; 10 c.c.). The cooled reaction product was poured into water, and the flocculent precipitate collected and thrice crystallised from ethanol, giving *nor-α-amyrenonol* as silky needles, m. p. 257—259°, $[\alpha]_D$ +34° (*c*, 0·89), which give a yellow coloration with tetranitromethane in chloroform (Found: C, 81·9; H, 11·0. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·8%). Acetylation of nor-α-amyrenonol with acetic anhydride in pyridine gave nor-α-amyrenonyl acetate as plates, m. p. 210—212° undepressed when mixed with the specimen described above.

Nor-α-amyrenonyl Acetate Oxide.—Nor-α-amyrenonyl acetate (75 mg.) in chloroform (10 c.c.) was treated with a solution of perbenzoic acid in chloroform (0·4N; 4·25 c.c.) and kept at 0° for 120 hours. After 5 days, absorption corresponding to 1·2 atoms of oxygen had occurred. The reaction mixture was washed with 2% sodium hydroxide and then with water. After the solution had been dried (Na_2SO_4), the solvent was removed under reduced pressure and the solid residue crystallised from ethanol, giving *nor-α-amyrenonyl acetate oxide* (30 mg.) as plates, m. p. 219—220° (Found: C, 76·3; H, 10·0. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%). Nor-α-amyrenonyl acetate oxide does not give a coloration with the tetranitromethane reagent nor does it exhibit high-intensity selective absorption in the ultra-violet.

Nor-β-amyrenonyl Acetate (with A. G. McInnes).—Acetylketo-oleanolic acid (1 g.) was refluxed for 8 hours in quinoline (50 c.c.). On cooling, the solution was poured into excess of hydrochloric acid (3%; 200 c.c.), and the mixture extracted with ether. The ethereal extract was washed with aqueous sodium hydroxide (5%; 400 c.c.), and water, and, after being dried ($MgSO_4$), was evaporated to dryness. The residue (0·75 g.) was dissolved in light petroleum, and the solution filtered through a column of activated alumina (Grade II; 25 g.). The column was then washed and fractions collected: fractions 1—10, with light petroleum (b. p. 60—80°; 1000 c.c.), giving 0·324 g. of eluate; fractions 11—13, with light petroleum–benzene (1 : 1; 300 c.c.), giving 0·335 g. of eluate; and fractions 14—16, with benzene (225 c.c.), giving 0·046 g. of eluate.

Fractions 1—10, 11—13, and 14—16 were crystallised separately from methanol giving long needles, m. p. 228—231°, 228—231°, and 226—230°, respectively, undepressed when intermixed. The three fractions were combined and crystallised from methanol, giving nor-β-amyrenonyl acetate as needles, m. p. 238—239°, $[\alpha]_D$ +50° (*c*, 0·53) (Found: C, 79·3; H, 10·5. Calc. for $C_{31}H_{48}O_3$: C, 79·4; H, 10·3%). It gives a yellow coloration with tetranitromethane in chloroform, and displays no high-intensity light absorption in the ultra-violet.

Methyl Acetyldihydroketoursolate.—(*a*) A solution of acetylursolic acid (5 g.) in glacial acetic acid (200 c.c.) was treated during 15 minutes with hydrogen peroxide (30%; 20 c.c.) in glacial acetic acid (20 c.c.), the mixture being stirred and heated on the steam-bath during the addition and for a further 2 hours. A second treatment with hydrogen peroxide (30%; 20 c.c.) in glacial acetic acid (20 c.c.) was made, and the mixture stirred at steam-bath temperature for 2 hours. The mixture was concentrated under reduced pressure to 50 c.c., cooled, and poured into water. The mixture was extracted with ether (3 × 40 c.c.), and the extract washed with sodium hydroxide solution (5%; 5 × 20 c.c.) and with water. The alkaline extract was acidified with dilute hydrochloric acid, and the precipitated solid (0·95 g.) collected, dissolved in ether, and esterified with an ethereal solution of diazomethane. The neutral fraction (0·75 g.), obtained in the usual manner, was dissolved in light petroleum (b. p. 60—80°; 200 c.c.) and filtered through a column of activated alumina (25 × 1·75 cm.). The column was washed, first with light petroleum (b. p. 60—80°)–benzene (1 : 1; 500 c.c.), giving 0·410 g. of eluate. A further 300 c.c. of the same solvent eluted material (0·120 g.) differing from the first and subsequent eluates (the latter obtained by washing the column with benzene and with methanol) by crystallising readily from ethanol. After three crystallisations from this solvent, methyl acetyldihydroketoursolate was obtained as fine needles, m. p. 246—249°, $[\alpha]_D$ +27° (*c*, 0·42) (Found: C, 75·1; H, 9·7. Calc. for $C_{33}H_{52}O_5$: C, 75·0; H, 9·9%) {Jeger, Borth, and Ruzicka, *loc. cit.*, give m. p. 248—250° (corr.), $[\alpha]_D$ +35°, and m. p. 246—248° (corr.), $[\alpha]_D$ +29°, for two specimens of methyl acetyldihydroketoursolate, the first of which was prepared by peroxide oxidation of acetylursolic acid followed by esterification, and the second by treatment of methyl acetylursolate with ozonised oxygen}.

(*b*) A solution of methyl acetylursolate (7·5 g.) in boiling glacial acetic acid (150 c.c.) was treated during 10 minutes with hydrogen peroxide (30%; 75 c.c.) in glacial acetic acid (75 c.c.). The mixture was refluxed for 2 hours, diluted to turbidity with water, and cooled. The fine needles which separated, after five recrystallisations from ethanol, gave methyl acetyldihydroketoursolate (4·4 g.) as needles, m. p. 250—253° (decomp.), $[\alpha]_D$ +25° (*c*, 0·92) (Found: C, 75·0; H, 9·8. Calc. for $C_{33}H_{52}O_5$: C, 75·0; H, 9·9%). The compound gave no coloration with tetranitromethane in chloroform, and was undepressed in m. p. when mixed with a specimen prepared by method (*a*).

Methyl Acetyldihydroketoisoursolate.—(*a*) A solution of methyl acetyldihydroketoursolate (0·75 g.) in chloroform (10 c.c.) and glacial acetic acid (40 c.c.) was treated with concentrated hydrochloric acid (2 c.c.), and kept at 40° for 30 minutes. The mixture was concentrated under reduced pressure, diluted with water, and extracted with ether. The extract was washed with dilute sodium carbonate solution and then with water, and dried (Na_2SO_4). A solution of the residue (0·52 g.), which crystallised from methanol, in light petroleum (b. p. 60—70°; 150 c.c.) was filtered through a column of activated alumina (13 × 1·75 cm.) which was then washed, first with light petroleum–benzene (1 : 1; 350 c.c.); the eluate was discarded. More of this solvent (400 c.c.) gave an eluate (80 mg.), m. p. 242—248°. Benzene (300 c.c.) then gave material (100 mg.), m. p. 246—253°, which was combined with the previous fraction and repeatedly crystallised from ethanol to yield *methyl acetyldihydroketoisoursolate* (70 mg.) as small prismatic needles, m. p. 253—256°, $[\alpha]_D$ +32° (*c*, 0·86) (Found: C, 75·3; H, 9·8. $C_{33}H_{52}O_5$ requires C, 75·0; H, 9·9%). A mixture of methyl acetyldihydroketoisoursolate and methyl acetyldihydroketoursolate (m. p. 250—253°) had m. p. 230—234°. Methyl acetyldihydroketoisoursolate does not give a coloration with tetranitromethane in chloroform, and exhibits an absorption maximum at 2890 Å (ε = 84).

The column was washed with more benzene (100 c.c.) (the small eluate was discarded), then with benzene–ether (1 : 1; 200 c.c.), and then with ether alone (100 c.c.). The eluates obtained by means of these solvents were combined and crystallised from ethanol, giving needles, m. p. 249—252° undepressed when mixed with methyl acetyldihydroketoursolate.

(*b*) A solution of methyl acetyldihydroketoursolate (0·50 g.) in glacial acetic acid (18 c.c.) was heated on a steam-bath for 6 hours with concentrated hydrochloric acid (10%; 0·5 c.c.). The mixture was kept at room temperature for 24 hours, and then diluted with water. The precipitate was collected and crystallised repeatedly from methanol and then from ethanol from which methyl acetyldihydroketoisoursolate separated as prismatic needles (0·085 g.), m. p. 254—256°, $[\alpha]_D$ +35° (*c*, 1·03), not depressed in m. p. when mixed with the specimen described under (*a*) (Found: C, 74·9; H, 10·2. Calc. for $C_{33}H_{52}O_5$: C, 75·0; H, 9·9%). Methyl acetyldihydroketoisoursolate was recovered unchanged after being refluxed for 10 hours with ethanolic hydroxylamine acetate.

Methyl Acetylbromodihydroketoursolate.—A solution of methyl acetyldihydroketoursolate (0·5 g.) in glacial acetic acid (60 c.c.) containing hydrogen bromide (0·2 c.c.; 47% solution in water), was treated dropwise with a solution of bromine in glacial acetic acid (3%; 5·5 c.c.) at room temperature with stirring. After 3 hours the mixture was poured into water. The precipitated solid was collected and crystallised thrice from aqueous acetone yielding *methyl acetylbromodihydroketoursolate* as needles, m. p. 126—128°; after being heated in a high vacuum for 1 hour at 55°, the bromo-ketone had m. p. 196—198°. Crystallisation of this high-melting form from acetone again gave needles, m. p. 126—128°, $[\alpha]_D$ +106° (*c*, 0·76). The bromo-ketone does not give a coloration with tetranitromethane in chloroform (Found: C, 64·9; H, 8·6. $C_{33}H_{51}O_5Br$ requires C, 65·2; H, 8·4%). Similar bromination of methyl acetyldihydroketoisoursolate gave the bromo-ketone as needles (from acetone), m. p. 118—122° not depressed when mixed with the specimen, m. p. 126—128°.

Methyl Acetylketoisoursolate.—(*a*) Methyl acetyldihydroketoursolate (0·5 g.) in glacial acetic acid (60 c.c.) was treated with an aqueous solution of hydrogen bromide (47%; 0·2 c.c.), and then at 60° with a solution of bromine in glacial acetic acid (3%; 5 c.c.) added dropwise, and with stirring. After the addition was complete, the solution was kept for 1 hour at 70°, and then poured into water. The solid was collected, washed with water, and crystallised four times from aqueous ethanol, giving methyl acetylketo*iso*ursolate (0·28 g.) as needles, m. p. 186—188°, $[\alpha]_D$ +87° (*c*, 0·81). Light absorption in ethanol: Maximum at 2490 Å, $\varepsilon = 15{,}500$. Methyl acetylketo*iso*ursolate does not give a coloration with tetranitromethane in chloroform.

(*b*) A solution of methyl acetylbromodihydroketoursolate (0·3 g.) in glacial acetic acid (15 c.c.) containing a trace of aqueous hydrogen bromide, was heated on a steam-bath for 3 hours. The solution was kept at room temperature for 12 hours and then poured into water, and the mixture extracted with ether. The extract was washed with dilute sodium carbonate solution and then with water, and dried (Na_2SO_4). After removal of the ether the residue was thrice crystallised from acetone, giving methyl acetylketo*iso*ursolate (0·2 g.) as needles, m. p. 186—188° undepressed when mixed with the specimen prepared by method (*a*); $[\alpha]_D$ +85° (*c*, 0·93) (Found: C, 74·9; H, 9·6. Calc. for $C_{33}H_{56}O_5$: C, 75·2; H, 9·6%). Light absorption in ethanol: Maximum at 2490 Å, $\varepsilon = 15{,}000$. Dreiding, Jeger, and Ruzicka (*loc. cit.*) report m. p. 193° (corr.), $[\alpha]_D$ +85°, for methyl acetylketo*iso*ursolate.

Hydrolysis of methyl acetylketo*iso*ursolate with 0·5% ethanolic potassium hydroxide gave methyl keto*iso*ursolate as plates, m. p. 236—238°, $[\alpha]_D$ +82° (*c*, 0·61) (Found: C, 76·5; H, 9·7. Calc. for $C_{31}H_{48}O_4$: C, 76·8; H, 9·9%). Light absorption in ethanol: Maximum at 2500 Å, $\varepsilon = 15{,}500$. Dreiding, Jeger, and Ruzicka (*loc. cit.*) give m. p. 240° (corr.), $[\alpha]_D$ +71°, for methyl keto*iso*ursolate.

The authors acknowledge assistance in various phases of this work from Mr. R. Bhuvanendram, B.Sc., and from Mr. J. T. Farquhar, B.Sc.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, July 13th*, 1951.]

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736. *Triterpene Resinols and Related Acids. Part XXIV.** 18-iso-β-*Amyranol.*

By RICHARD BUDZIAREK, WILLIAM MANSON, and F. S. SPRING.

Treatment of β-amyrenonyl benzoate (VIII; R = Bz, R′ = Me) with alkali is shown to give 18-*iso*-β-amyrenonol (XI; R = H). Catalytic hydrogenation of 18-*iso*-β-amyrenonyl acetate yields 18-*iso*-β-amyrin acetate (XII; R = Ac), oxidation of which with hydrogen peroxide yields a saturated ketone, 18-*iso*-β-amyranonyl acetate (XV; R = Ac). Reduction of the latter by the Kishner–Wolff procedure gives 18-*iso*-β-amyranol (XVI; R = H) which differs from the saturated pentacylic triterpenoid alcohols hitherto described.

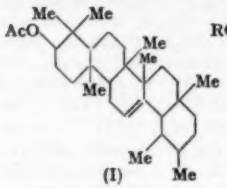
OXIDATION of β-amyrin acetate with chromic anhydride in acetic acid gives an 8% yield of acetone, isolated as its 2 : 4-dinitrophenylhydrazone. Similar oxidation of α-amyrin acetate does not give acetone. The triterpenoid acetates employed were purified to constant optical rotation, and were rigorously dried; a common batch of purified acetic acid was employed and the oxidations were effected under as far as possible identical conditions. The structures ascribed to the α- (I) and the β- (II; R = Ac) acetate differ only in the nature of ring E, and there is evidence that they are sterically identical at $C_{(5)}$, $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, and possibly at $C_{(14)}$.

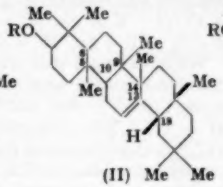
Ames, Halsall, and Jones (*J.*, 1951, 450) have shown that lupenyl acetate (III; R = Ac), which contains an *iso*propenyl group attached to ring E, is isomerised by mineral acid to δ-amyrin acetate (IV), itself obtained from β-amyrin acetate by a two-stage process. It has been established (Davy, Halsall, and Jones, *Chem. and Ind.*, 1951, 233; Barton and Holness, *Chem. and Ind.*, 1951, 233) that rings D/E in lupeol (III; R = H) are *trans*-fused and that the rings D/E in β-amyrin (II; R = H) are *cis*-fused. Consequently, structural differences apart, lupanol (dihydrolupeol) (V) and β-amyranol (dihydro-β-amyrin) (VI) differ in orientation around $C_{(18)}$. Before attempting to assess the significance of the formation of acetone from β-amyrin acetate, we considered it essential to prepare 18-*iso*-β-amyranol (VII) in order to compare it with lupanol and other saturated pentacyclic triterpenoid alcohols.

A simple route to 18-*iso*-β-amyranol appeared to be available since indications existed in the literature that epimerisation at $C_{(18)}$ in β-amyrenonol could be achieved. Thus in a discussion

* Part XXIII, preceding paper.

concerning the physical constants of β-amyrenonol and its esters, Ruzicka, Müller, and Schellenberg (*Helv. Chim. Acta*, 1939, **22**, 758) reported that treatment of β-amyrenonol (m. p. 230—231°, $[\alpha]_D$ +102°) (VIII; R = H, R′ = Me) for a prolonged period with 10% alcoholic


(I)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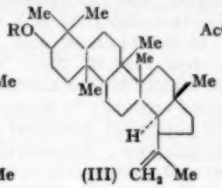
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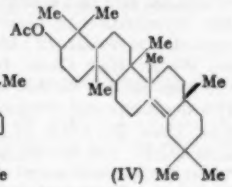
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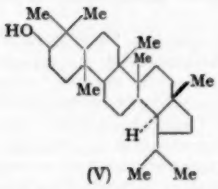
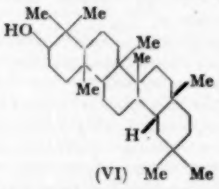

(V) Me Me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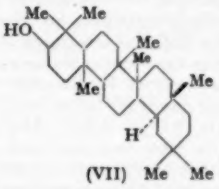
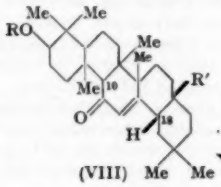
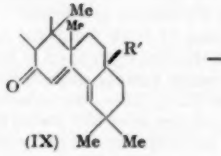

(VII) Me Me

alkali gave an isomer, m. p. 247—248°, $[\alpha]_D$ +81·5°. This isomerisation could involve either $C_{(10)}$ or $C_{(18)}$ or both centres simultaneously, but the fact that bromination of β-amyrenonyl acetate (VIII; R = Ac, R′ = Me) proceeds smoothly to give β-amyradienonyl acetate (Picard


(VIII) Me Me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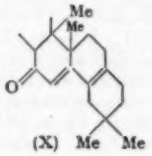
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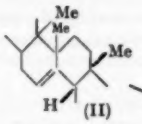
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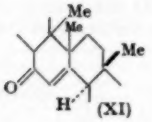
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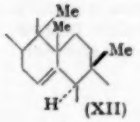
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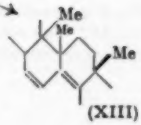
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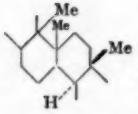
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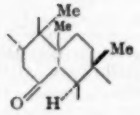
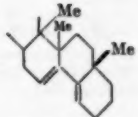

(XV)


(XIV) Me Me

and Spring, *J.*, 1941, 35) (IX; R = Ac, R′ = Me) suggests that enolisation of β-amyrenonyl acetate involves $C_{(18)}$. Furthermore, reduction of β-amyradienonyl acetate by using sodium ethoxide and hydrazine gave a complex mixture from which an *allo*-β-amyrenonyl acetate was

obtained; this probably differs from β-amyrenonyl acetate in the orientation around $C_{(18)}$ (Green, Mower, Picard, and Spring, *J.*, 1944, 527). Kitasato (*Acta Phytochim.*, 1934—1935, **8**, 1, 315) has shown that methyl acetylketo-oleanolate (VIII; R = Ac, R′ = CO_2Me) is isomerised by mineral acid to a *ψ*-isomer; that this isomerisation also involves $C_{(18)}$ is indicated by the fact that bromination of acetylketo-oleanolic acid (VIII; R = Ac, R′ = CO_2H) gives the conjugated acetyllolean-12 : 18-dien-11-onolic acid (IX; R = Ac, R′ = CO_2H) (Ruzicka, Jeger, and Winter, *Helv. Chim. Acta*, 1943, **26**, 265). We have found that when melted, the dienone-acid loses carbon dioxide rapidly to give nor-β-amyradienonyl acetate (X; R = Ac) identical with the compound obtained originally by Ruzicka, Cohen, Furter, and Sluys-Veer (*Helv. Chim. Acta*, 1938, **21**, 1735) by prolonged treatment of acetylketo-oleanolic acid (VIII; R = Ac, R′ = CO_2H) with boiling quinoline. The ease of decarboxylation of the dienone-acid indicates that it is a βγ-unsaturated acid and that it is correctly formulated as (IX; R = Ac, R′ = CO_2H). Barton and Holness (*loc. cit.*) have recently reported that the alkali isomerisation of methyl acetylketo-oleanolate involves inversion at $C_{(18)}$.

We find that treatment of β-amyrenonyl benzoate with strong alcoholic alkali gives in high yield an isomeric β-amyrenonol which shows the characteristic light-absorption properties of an αβ-unsaturated ketone and was characterised by the formation of its acetate. The reactions described below establish that this αβ-unsaturated keto-acetate is 18-*iso*-β-amyrenonyl acetate (XI; R = Ac). 18-*iso*-β-Amyrenonyl acetate was recovered unchanged after treatment with bromine in acetic acid under conditions which led to the conversion of β-amyrenonyl acetate or acetylketo-oleanolic acid into the corresponding conjugated dienones (IX). Catalytic reduction of 18-*iso*-β-amyrenonyl acetate at room temperature gives in high yield an isomeric β-amyrin acetate, the relationship of which to β-amyrin acetate (II; R = Ac) was established by its easy oxidation with selenium dioxide to β-amyradienyl-II acetate. Of the two possible structures (XIII; R = Ac) and (XIV; R = Ac) previously considered for the last compound, first prepared by Ruzicka, Müller, and Schellenberg (*Helv. Chim. Acta*, 1939, **22**, 767) by the oxidation of β-amyrin acetate (II; R = Ac) with selenium dioxide, Barton and Brooks (*J.*, 1951, 257) have shown that the former is correct. The formation of β-amyradienyl-II acetate (XIII; R = Ac) by oxidation of both β-amyrin acetate and the isomeric β-amyrin acetate described above proves that the last compound is 18-*iso*-β-amyrin acetate (XII; R = Ac).

Oxidation of 18-*iso*-β-amyrin acetate with hydrogen peroxide gives a saturated ketone, 18-*iso*-β-amyranonyl acetate (XV; R = Ac), which is not isomerised by either mineral acid or strong alkali, and represents the sterically stable isomer in so far as the orientation at $C_{(18)}$ is concerned. Treatment of 18-*iso*-β-amyranonyl acetate with bromine gives bromo-18-*iso*-β-amyranonyl acetate. This is considerably more stable than the isomeric bromo-β-amyranonyl acetate, obtained by similar bromination of β-amyranonyl acetate, which readily loses hydrogen bromide when warmed with acetic acid, giving *iso*-β-amyrenonyl acetate (Seymour and Spring, *J.*, 1941, 319); bromo-18-*iso*-β-amyranonyl acetate is recovered unchanged after prolonged heating in glacial acetic acid.

Reduction of 18-*iso*-β-amyranonyl acetate by using the Kishner–Wolff method, followed by acetylation, gives 18-*iso*-β-amyranyl acetate (XVI; R = Ac), hydrolysis of which gives 18-*iso*-β-amyranol, which differs from previously described saturated pentacyclic triterpenoid alcohols. The constants of β-amyranol, lupanol, and taraxastanol (heterolupanol) are shown below, together with those of 18-*iso*-β-amyranol.

	Alcohol		Acetate	
	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
β-Amyranol [1]	186—186·5°	+18·5°	284·5—285°	+21°
Lupanol [2]	201—202	−17·8	245—246	−1·8
Taraxastanol (Heterolupanol) [3]	218—220	+11	262—263	+23
18-*iso*-β-Amyranol [4]	229—230	+36	280—282	+44

[1] Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1178. [2] Heilbron, Kennedy, and Spring, *J.*, 1938, 329. [3] Lardelli and Jeger, *Helv. Chim. Acta*, 1948, **31**, 813; Lardelli, Jeger, Krüsi, and Ruzicka, *ibid.*, p. 1159. [4] This paper.

The orientation at $C_{(18)}$ in the two isomers, β-amyranol and 18-*iso*-β-amyranol, in each case represents the sterically stable configuration since neither β-amyranonol nor 18-*iso*-β-amyranonol is isomerised at $C_{(18)}$ under strongly acid or alkaline conditions. There is furthermore a strong *prima facie* case for a common $C_{(18)}$-configuration in β-amyranol, 18-*iso*-β-amyranol, germanicol [cf. the conversion of siaresinolic acid into morolic acid (Barton, Brooks, and Holness,

J., 1951, 278)], and lupeol [cf. the conversion of betulin into moradiol diacetate (Davy, Halsall, and Jones, *Chem. and Ind.*, 1950, 732)].

The non-identity of 18-*iso*-β-amyranol and lupanol leads us to the conclusion that the acetone obtained by oxidation of β-amyrin acetate originates in the *gem*-dimethyl group in ring E.

Experimental.

M. p.s are corrected; rotations (1-dm. tube) are for chloroform solutions at room temperatures and are approximated to the nearest degree.

Oxidation of β-Amyrin Acetate.—A solution of β-amyrin acetate [m. p. 240—241°, $[\alpha]_D$ +83° (*c*, 1·67)] (10 g.) in purified glacial acetic acid (600 c.c.) was gently boiled to effect slow distillation of the solvent. A solution of chromic anhydride (30 g.) in 80% acetic acid (100 c.c.) was added dropwise. The distillate was collected in fractions of approximately 40 c.c. Each of the fractions was neutralised with sodium hydroxide solution and redistilled. The first 2—3 c.c. of distillate from each fraction was treated with a solution of 2 : 4-dinitrophenylhydrazine in hydrochloric acid, and the yellow solid collected. After nine such fractions had been collected (134 mg. of dinitrophenylhydrazone), the reaction mixture was diluted with purified acetic acid (100 c.c.), and the distillation continued. Since treatment of fractions 9 and 10 gave only a trace of 2 : 4-dinitrophenylhydrazone, the reaction mixture was treated with a solution of chromic anhydride (10 g.) in water (10 c.c.) and purified acetic acid (50 c.c.), and the distillation continued, giving fractions 12—17, each of which, on treatment as described above, gave a 2 : 4-dinitrophenylhydrazone. The reaction mixture was diluted with purified acetic acid, and the distillation continued until the distillate gave a negative carbonyl reaction (fraction 20). The mixture was again treated with chromic anhydride (10 g.) in water (10 c.c.) and glacial acetic acid (100 c.c.), and the distillation continued to give fractions 21—26, the reaction mixture being diluted with acetic acid after the collection of fraction 23. Treatment of fractions 11—26 as described above gave a 2 : 4-dinitrophenylhydrazone (270 mg.). Further treatment of the reaction mixture with chromic acid gave distillates free from carbonyl component. The combined crops of 2 : 4-dinitrophenylhydrazone (404 mg.; 7·9%) were crystallised from ethanol, yielding acetone 2 : 4-dinitrophenylhydrazone as orange needles, m. p. 125—127° undepressed when mixed with an authentic specimen (Found: C, 45·5; H, 4·3; N, 24·0. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2; N, 23·5%).

Acetone was not detected in the distillates obtained from an exactly similar oxidation of α-amyrin acetate in which the same batch of purified acetic acid was employed or in the distillates obtained from a blank experiment.

β-Amyrenonyl Benzoate.—A solution of β-amyrin benzoate (40 g.) in boiling purified glacial acetic acid (2 l.) was treated with a solution of chromic anhydride (40 g.) in water (10 c.c.) and glacial acetic acid (800 c.c.) added dropwise during 1 hour. The solution was boiled for 1·5 hours, after which time it was treated with boiling water (1200 c.c.) with vigorous stirring. Next morning the crystalline solid was collected, washed with aqueous methanol, and dried (21 g.; m. p. 261—263°). Crystallisation from chloroform–methanol gave β-amyrenonyl benzoate as prismatic needles, m. p. 269—270·5°, $[\alpha]_D$ +112° (*c*, 1·85) (Found: C, 81·1; H, 9·7. Calc. for $C_{37}H_{52}O_3$: C, 81·6; H, 9·6%). β-Amyrenonyl benzoate does not give a coloration with tetranitromethane in chloroform. Light absorption in ethanol: Maximum at 2300 Å (ε = 21,500) and an inflection at 2520 Å (ε = 13,800).

18-iso-*β-Amyrenonol* (XI; R = H).—A solution of β-amyrenonyl benzoate (14·7 g.) in 15% ethanolic potassium hydroxide (1200 c.c.) was heated under reflux for 52 hours. The pale yellow solution was concentrated to half-bulk and diluted with water. The solid was collected, washed with water until the washings were neutral (litmus), and dried (11·8 g.). Crystallisation from methanol gave 18-iso-*β-amyrenonol* as long plates, m. p. 254—255°, $[\alpha]_D$ +84° (*c*, 0·74) (Found: C, 81·3; H, 11·0. $C_{30}H_{48}O_2$ requires C, 81·8; H, 11·0%). Light absorption in ethanol: Maximum at 2440 Å (ε = 12,300). The alcohol, m. p. 247—248°, $[\alpha]_D$ +81·5°, obtained by Ruzicka, Müller, and Schellenberg (*Helv. Chim. Acta*, 1939, **22**, 758) by the action of alkali on β-amyrenonol is probably 18-*iso*-β-amyrenonol.

18-iso-*β-Amyrenonyl Acetate* (XI; R = Ac).—Acetylation of 18-*iso*-β-amyrenonol by heating it with pyridine (4 parts) and acetic anhydride (6 parts) on the steam-bath for 2·5 hours gave 18-iso-*β-amyrenonyl acetate* which separated from chloroform–methanol as hard, square, squat prisms, m. p. 277·5—279°, $[\alpha]_D$ +75° (*c*, 1·8) (Found: C, 79·8; H, 10·8. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). Light absorption in ethanol: Maximum at 2450 Å (ε = 10,100). A mixture of 18-*iso*-β-amyrenonyl acetate and β-amyrenonyl acetate (m. p. 265—266°) had m. p. 254—256°, and a mixture of 18-*iso*-β-amyrenonyl acetate and α-amyrenonyl acetate (m. p. 275°) had m. p. 228—230°. The *allo*-β-amyrenonyl acetate [m. p. 262—265°, $[\alpha]_D$ +67° (pyridine), $\lambda_{max.}$ 2460 Å (ε = 11,000)] described by Green, Mower, Picard, and Spring (*loc. cit.*) is almost certainly a somewhat impure specimen of 18-*iso*-β-amyrenonyl acetate; like the latter, it was recovered unchanged after treatment with bromine in acetic acid.

18-iso-*β-Amyrin Acetate* (XII; R = Ac).—A solution of 18-*iso*-β-amyrenonyl acetate (1·0 g.) in glacial acetic acid (180 c.c.) was added to a suspension of freshly reduced platinum (from 300 mg. of platinic oxide) in acetic acid (15 c.c.), and the mixture shaken with hydrogen at room temperature. After 24 hours the reaction product separated as plates, and after 40 hours the absorption of hydrogen was complete (approximately 2 mols.). The mixture was heated to dissolve the product and filtered to remove platinum. The filtrate was concentrated under reduced pressure to approximately 60 c.c., and, after cooling, the separated solid was collected, washed with cold methanol, and dried. Recrystallisation from methanol–chloroform gave 18-iso-*β-amyrin acetate* as plates (740 mg.), m. p. 245—246·5°, $[\alpha]_D$ +53° (*c*, 0·96) (Found: C, 82·25; H, 11·2. $C_{32}H_{52}O_3$ requires C, 82·0; H, 11·2%). 18-*iso*-β-Amyrin acetate gives a bright yellow colour with the tetranitromethane reagent and does not exhibit selective absorption in the ultra-violet. A mixture of 18-*iso*-β-amyrin acetate with β-amyrin acetate

(m. p. 241—242°) had m. p. 218—222°, and a mixture of 18-*iso*-β-amyrin acetate with *iso*-β-amyrin acetate (2-acetoxyolean-10-ene) (m. p. 250—251°) had m. p. 212—220°.

*β-Amyradienyl-*II *Acetate* (XIII; R = Ac).—A solution of 18-*iso*-β-amyrin acetate (220 mg.) in boiling acetic acid (20 c.c.) was treated with a solution of selenium dioxide (200 mg.) in water (0·5 c.c.) and glacial acetic acid (10 c.c.) added dropwise during 20 minutes, and the mixture refluxed for 1 hour. Freshly fused sodium acetate (1 g.) was added and the refluxing continued for 20 minutes. The hot mixture was filtered through sintered glass, the filtrate diluted with water, and the precipitated solid collected, washed with water, and dried. A solution of the solid in ether was washed with 3% aqueous potassium cyanide and with water, and dried. The residue obtained after removal of the solvent was twice crystallised from methanol–chloroform, giving β-amyradienyl-II acetate (150 mg.) as plates, m. p. 225·5—227°, $[\alpha]_D$ −63° (*c*, 1·01); the m. p. was not depressed when the acetate was mixed with a specimen (m. p. 228°) obtained by the same method starting from β-amyrin acetate. Light absorption in ethanol: Maxima at 2510 (ε = 29,100), 2430 (ε = 27,300), and 2600 Å (ε = 19,500). Ruzicka, Müller, and Schellenberg (*Helv. Chim. Acta*, 1939, **22**, 767) give m. p. 228—229°, $[\alpha]_D$ −62°, for β-amyradienyl-II acetate.

18-iso-*β-Amyranonyl Acetate* (XV; R = Ac).—A solution of 18-*iso*-β-amyrin acetate (0·7 g.) in glacial acetic acid (200 c.c.), heated on a boiling-water bath with stirring, was treated with a solution of hydrogen peroxide (30%; 20 c.c.) in glacial acetic acid (20 c.c.) added dropwise during 15 minutes. The solution was maintained at the same temperature for 2 hours and again treated with a solution of hydrogen peroxide (30%; 15 c.c.) in acetic acid (15 c.c.) added during 15 minutes. After being stirred for 1 hour on the boiling-water bath, the solution was treated dropwise with boiling water with vigorous stirring until crystallisation commenced. Next morning the solid was collected, washed with aqueous methanol, and dried (m. p. 276—283°, 250 mg.). A solution of the solid in benzene (20 c.c.) was filtered through a column of alumina (Brockmann Grade I/II; 1·5 × 5 cm.) and the column washed with benzene (60 c.c.). The benzene filtrate was evaporated to dryness and the solid residue (180 mg.), after crystallisation from methanol–chloroform and then from methanol, gave 18-iso-*β-amyranonyl acetate* as plates, m. p. 286—287°, $[\alpha]_D$ +77° (*c*, 1·22) (Found: C, 79·5; H, 10·8. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). In four different oxidations of 18-*iso*-β-amyrin acetate the yield of pure 18-*iso*-β-amyranonyl acetate varied between 22% and 26%. A mixture of 18-*iso*-β-amyranonyl acetate (m. p. 286—287°) with β-amyranonyl acetate (m. p. 300°) did not show a marked depression in m. p. (284—290°). Light absorption in ethanol: Inflection at 3000 Å (ε = 126).

A solution of 18-*iso*-β-amyranonyl acetate (90 mg.) in chloroform (0·5 c.c.)–glacial acetic acid (10 c.c.) was treated with 3 drops of concentrated hydrochloric acid and kept at 35—45° for 1 hour. The reaction mixture gave 18-*iso*-β-amyranonyl acetate (80 mg.) as plates, m. p. 286—287°, $[\alpha]_D$ +77° (*c*, 1·15), after one crystallisation from methanol.

18-iso-*β-Amyranonol* (XV; R = H).—A solution of 18-*iso*-β-amyranonyl acetate (m. p. 284—285°; 300 mg.) in 15% ethanolic potassium hydroxide (60 c.c.) was refluxed for 50 hours. The prismatic needles separating on cooling were collected, washed with methanol, and dried (180 mg.; m. p. 308—310°). Recrystallisation from methanol containing a trace of acetic acid and then from methanol gave 18-iso-*β-amyranonol* (110 mg.) as prismatic rods, m. p. 309—310°, $[\alpha]_D$ +91° (*c*, 1·07) (Found: C, 81·3; H, 11·45. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Light absorption in ethanol: Inflection at 3000 Å (ε = 40). The alkaline mother-liquor was diluted with water and the precipitated solid collected, dried, and acetylated by using pyridine (2 c.c.) and acetic anhydride (1 c.c.). Crystallisation of the product from chloroform–methanol gave 18-*iso*-β-amyranonyl acetate (90 mg.) as elongated plates, m. p. 284—285°, $[\alpha]_D$ +77° (*c*, 0·70), undepressed in m. p. when mixed with the starting material.

Acetylation of 18-*iso*-β-amyranonol (m. p. 309—310°; 60 mg.), by using acetic anhydride and pyridine in the usual manner, gave 18-*iso*-β-amyranonyl acetate (50 mg.) as elongated plates, m. p. 287—288·5°, $[\alpha]_D$ +78° (*c*, 0·84), unchanged by a recrystallisation from the same solvent, and undepressed in m. p. when mixed with a specimen of the starting material. Light absorption in ethanol: Maximum at 3000 Å (ε = 140).

Bromo-18-iso-*β-amyranonyl Acetate*.—A solution of 18-*iso*-β-amyranonyl acetate (250 mg.; m. p. 284·5—286°) in glacial acetic acid (20 c.c.) was treated with a solution of bromine in glacial acetic acid (5%; 1·2 mol.) added during 1 hour at 65—80°. The solution was maintained at 80° for 3 hours and then diluted with water, and the solid collected, washed with water, dried, and crystallised from methanol–chloroform. The first crop (160 mg.) separated as plates, m. p. 245—246° (decomp.), $[\alpha]_D$ +17·5° (*c*, 1·15), which did not give a coloration with tetranitromethane in chloroform and gave a positive halogen test. From the mother-liquors a second crop (65 mg.) of flat needles, m. p. 260—265° (decomp.), separated. The first crop was heated on the steam-bath for 3½ hours with glacial acetic acid. On concentration and cooling of the solution, *bromo*-18-iso-*β-amyranonyl acetate*, separated as plates, m. p. 249—250° (decomp.) unchanged by two recrystallisations from methanol–chloroform, $[\alpha]_D$ +18° (*c*, 1·06) (Found: C, 68·4; H, 9·1. $C_{32}H_{51}O_3Br$ requires C, 68·2; H, 9·1%). Light absorption in ethanol: Maximum at 3100 Å (ε = 155). Similar treatment (heating with acetic acid) of the second crop gave elongated plates, m. p. 276—278° undepressed when mixed with 18-*iso*-β-amyranonyl acetate, $[\alpha]_D$ +73° (*c*, 0·93). Light absorption in ethanol: Maximum at 2900 Å (ε = 50). The physical properties of this fraction show that it is essentially 18-*iso*-β-amyranonyl acetate contaminated with the bromo-ketone described above.

18-iso-*β-Amyranyl Acetate* (XVI; R = Ac).—A mixture of 18-*iso*-β-amyranonyl acetate (m. p. 284—285·5°; 300 mg.), alcoholic sodium ethoxide (from 750 mg. of sodium and 10 c.c. of ethanol), and hydrazine hydrate (2 c.c.; 100%) was heated in an autoclave at 200° for 17 hours. The cooled mixture was diluted with water and extracted with ether. The extract was washed successively with hydrochloric acid (3%) and water and dried. After removal of the solvent, the solid residue was heated on the steam-bath for 2 hours with pyridine (3 c.c.) and acetic anhydride (2 c.c.). The crystalline solid separating on

cooling was collected, washed with methanol, and dried (155 mg.; m. p. 277—279°). A second crop (m. p. 263—266°; 25 mg.) was undepressed in m. p. when mixed with the first crop. The first crop was twice recrystallised from methanol–chloroform, giving 18-iso-β-*amyranyl acetate* as plates, m. p. 280—282°, $[\alpha]_D$ +43° (*c*, 0·88) (Found: C, 81·6; H, 11·7. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%). 18-*iso*-β-Amyranyl acetate does not give a colour with tetranitromethane in chloroform. A mixture of 18-*iso*-β-amyranyl acetate with β-amyranyl acetate (m. p. 284°) had m. p. 256—262°, and a mixture with lupanyl acetate (m. p. 246—248°) had m. p. 233—237°.

The original mother-liquors from 18-*iso*-β-amyranyl acetate deposited on long storage a crop of large prisms (40 mg.), m. p. 179—180°, recrystallisation of which from methanol gave prismatic needles, m. p. 180—181°, $[\alpha]_D$ −5° (*c*, 1·11) (Found: C, 81·1; H, 11·6. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). The *substance* gives a very faint yellow coloration with the tetranitromethane reagent, and it does not show selective absorption in the ultra-violet region of the spectrum.

18-iso-β-*Amyranol* (XVI; R = H).—Hydrolysis of 18-*iso*-β-amyranyl acetate (90 mg.) was effected by heating it under reflux with 3% alcoholic potassium hydroxide for 6 hours. The product, isolated in the usual manner, separated from ethanol as plates (50 mg.), m. p. 228—229°, which after two crystallisations from methanol–chloroform gave 18-iso-β-*amyranol* as flat prisms (thick plates), m. p. 229—230°, $[\alpha]_D$ +36° (*c*, 1·21) (Found: C, 83·85; H, 12·4. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%). Acetylation of 18-*iso*-β-amyranol (30 mg.) by warming it on the steam-bath for 3 hours with pyridine (1 c.c.) and acetic anhydride (1 c.c.) gave 18-*iso*-β-amyranyl acetate (25 mg.) as plates (from methanol), m. p. 280—282° undepressed when mixed with the specimen described above, $[\alpha]_D$ +44° (*c*, 1·11).

Decarboxylation of Acetylolean-12 : 18-dien-11-onolic Acid (IX; R = Ac, R′ = CO_2H). *Nor-*β*-amyradienonyl Acetate* (X) (With L. C. McKean).—Acetylolean-12 : 18-dien-11-onolic acid (250 mg.; m. p. 287—288°), prepared by Ruzicka, Jeger, and Winter's method (*loc. cit.*), was heated in an atmosphere of nitrogen at 285—295°. After 5 minutes, when evolution of carbon dioxide had ceased, the mixture was cooled and dissolved in ether. The solution was washed with 5% sodium hydroxide solution and then with water, and dried ($MgSO_4$). After removal of the ether, a solution of the residue (184 mg.) in light petroleum (b. p. 60—80°; 100 c.c.) was filtered through a column of activated alumina (Grade II). After the column had been washed with light petroleum (200 c.c.) and light petroleum–benzene (7 : 1; 100 c.c.), eluates were obtained by washing it with light petroleum–benzene (4 : 1; 100 c.c.), light petroleum–benzene (1 : 1; 500 c.c.), and ether (100 c.c.); these were combined (75 mg.) and thrice crystallised from methanol, giving nor-β-amyradienonyl acetate as prisms, m. p. 203—205°, $[\alpha]_D$ +144° (*c*, 1·23) (Found: C, 80·0; H, 10·1. Calc. for $C_{31}H_{44}O_3$: C, 79·8; H, 9·9%). Nor-β-amyradienonyl acetate gave a bright yellow coloration with tetranitromethane in chloroform, and showed a light-absorption maximum in ethanol at 2970 Å (ε = 22,000). Ruzicka, Jeger, and Winter (*loc. cit.*) report m. p. 202°, $[\alpha]_D$ +150°, and light-absorption maximum at 2970 Å (ε = 22,400), for nor-β-amyradienonyl acetate, obtained by treatment of acetylketo-oleanolic acid with boiling quinoline.

Acidification of the alkaline washings of the ethereal extract, followed by crystallisation of the product from methanol–chloroform, yielded unchanged acetylolean-12 : 18-dien-11-onolic acid (28 mg.), m. p. 283—285° undepressed when mixed with the starting material.

The Royal Technical College, Glasgow. [*Received, July 13th*, 1951.]

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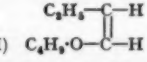
737. *Preparation and Infra-red Spectra of the Geometrical Isomers of But-1-enyl Butyl Ether.*

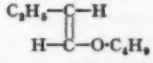
By R. H. Hall, A. R. Philpotts, E. S. Stern, and W. Thain.

But-1-enyl butyl ether, prepared by the catalysed vapour-phase thermal fission of butaldehyde dibutyl acetal, was separated into geometrical isomers by distillation. The constitution of both isomers was proved, and structural isomerism excluded, by hydrogenation to di-*n*-butyl ether and by hydrolysis with cold dilute mineral acid to butaldehyde. The *cis*-configuration was assigned to the lower-boiling, and the *trans*-structure to the higher-boiling isomer, on the basis of infra-red absorption data.

During the preparation of but-1-enyl butyl ether, which was required in another investigation, the *cis*- and the *trans*-isomer (I and II, respectively) were separated and characterised. The infra-red absorption spectra of the isomers were also recorded and showed certain interesting features.



(I)



(II)

Thermal fission of butaldehyde dibutyl acetal in the vapour phase at 350° in the presence of *iso*propylsulphate and quinoline (cf. Bramwyche, Mugdan, and the Distillers Co., Ltd.,

B.P. 603,471) yielded a mixture of butanol and the desired ether which could not be separated into its constituents by simple fractional distillation owing to the formation of a constant-boiling mixture; the butanol was readily removed, however, by repeated washing with dilute sodium hydrogen carbonate solution. In view of the possibility that the residual oil might be a mixture of geometrical isomers, it was submitted to precise fractional distillation under reduced pressure ; two substances, b. p. 35·5°/10·5 mm. and b. p. 41·5°/10 mm., were obtained, which were identified as (I) and (II), respectively, in the following manner.

Both compounds had the composition $C_8H_{16}O$ and absorbed one mol. of hydrogen on catalytic hydrogenation with the formation of di-*n*-butyl ether. These facts, taken in conjunction with the mode of formation of the compounds, proved that the latter were isomeric butenyl butyl ethers. The possibility that the ethylenic linkage was not in the 1 : 2-position in one of the isomers was excluded by the formation of butaldehyde *p*-nitro- and 2 : 4-dinitro-phenylhydrazone from each substance on treatment of either with aqueous-alcoholic mineral acid

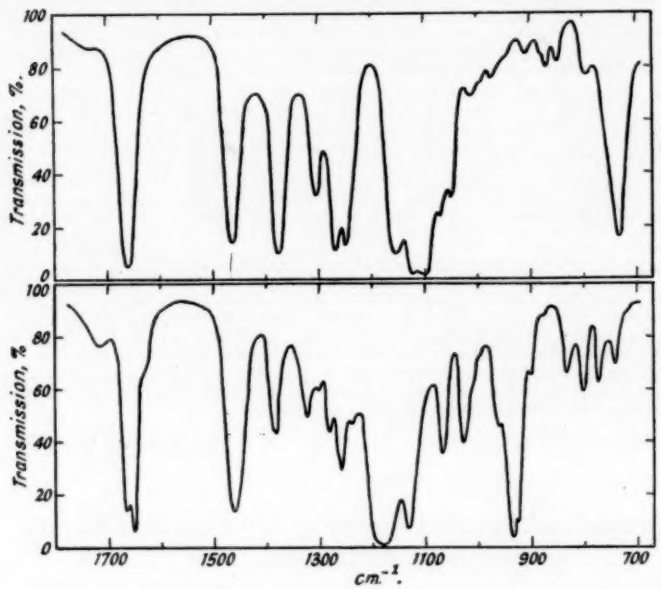


FIG. 1*a*.
cis-*But-1-enyl butyl ether*

FIG. 1*b*.
trans-*But-1-enyl butyl ether*

solutions of *p*-nitro- and 2 : 4-dinitro-phenylhydrazine, respectively. The compounds were thus *cis-trans*-isomers of but-1-enyl butyl ether and the final assignment of structure was based on their infra-red absorption spectra.

The CH deformation frequencies in the near infra-red have been used (Sheppard and Sutherland, *Proc. Roy. Soc.*, 1949, **196**, 195) to establish the substitution round an ethylenic double bond. In particular, frequencies near 970 cm.$^{-1}$ and 700 cm.$^{-1}$ were shown to be characteristic of *trans*- and *cis*-substituted ethylenes, respectively, in hydrocarbons (Andersen and Seyfried, *Analyt. Chem.*, 1948, **20**, 998) and in alcohols where the double bond is separated from the hydroxyl group (Crombie and Harper, *J.*, 1950, 873; Sondheimer, *ibid.*, p. 877). The spectra of crotonaldehyde, crotonic acid, and crotyl alcohol (Philpotts and Thain, to be published) all have a strong band near 970 cm.$^{-1}$ so it is possible that this particular identification rule also applies when an oxygenated group is close enough to the double bond to influence it. The rule is, in fact, used here to assign the *cis*-configuration to the lower-boiling isomer and the *trans*-configuration to the higher-boiling one.

The spectra are shown in the figures. That of the lower-boiling isomer (Fig. 1*a*) has a broad band at 733 cm.$^{-1}$ compared with 720 cm.$^{-1}$ and 725 cm.$^{-1}$ reported for *cis*-unsaturated alcohols (Crombie and Harper, *loc. cit.*; Sondheimer, *loc. cit.*); since this spectrum (Fig. 1*a*) has no strong band between 850 and 1030 cm.$^{-1}$ the identification as the *cis*-isomer is certain. In the spectrum

of the higher-boiling isomer (Fig. 1*b*) the only band of sufficiently high intensity to be the "*trans*-band" is at 933 cm.$^{-1}$. This frequency is surprisingly low but the absence of strong absorption near 700 cm.$^{-1}$ does give further evidence that the higher-boiling compound is indeed the *trans*-isomer.

The C=C stretching mode absorption is very much stronger in the spectra of the 5-oxanon-3-ene isomers than in those of hydrocarbons of the corresponding type. This increased intensity is also shown in spectra of unsubstituted vinyl ethers, *e.g.*, ethyl vinyl ether ("Nat. Bur. Stand. Catalog of Spectra," No. 143) and butyl vinyl ether (unpublished data of the authors). The *trans*-isomer of but-1-enyl butyl ether has a double band in this region whilst the *cis*-isomer has a single band; this behaviour is similar to that of the hydrocarbons and the frequencies are also similar (~1660 cm.$^{-1}$). On the other hand the unsubstituted vinyl ethers have a shifted (double) C=C band at 1620 cm.$^{-1}$ compared with the single one near 1640 cm.$^{-1}$ given by Δ^1-olefins.

Conversion of either isomer into di-*n*-butyl ether results, as expected, in the disappearance of the strong bands characteristic of the olefinic double bond, the saturated ether showing no strong absorption between 700 and 1050 cm.$^{-1}$ or between 1500 and 1700 cm.$^{-1}$.

Experimental.

All m. p.s and b. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss of Oxford.

The infra-red spectra were recorded (a rock-salt prism being used) on a Perkin–Elmer spectrometer with General Motors Amplifier and Brown Recorder. Lithium fluoride and glass shutters were used at appropriate frequencies with no other correction for scattered radiation. The solutions were 20% by volume in carbon tetrachloride for the range 840—1800 cm.$^{-1}$ and in *cyclo*hexane for the range 650—840 cm.$^{-1}$. The cell was approximately 0·1 mm. thick.

Preparation of Butaldehyde Dibutyl Acetal.—A mixture of butaldehyde (250 g.), butanol (1110 g.), concentrated hydrochloric acid (10 c.c.), and methylene dichloride (250 c.c.) was distilled rapidly up a 3-ft. Vigreux column fitted with a phase-separating still-head which continuously decanted the upper (aqueous) layer in the distillate and returned the lower layer to the column as reflux. When no more aqueous layer was being formed (after *ca.* 24 hours) the reaction mixture was cooled, treated with anhydrous sodium acetate (10 g.), and rapidly distilled to free the product from inorganic salts. Subsequent fractionation of the distillate afforded butaldehyde dibutyl acetal (547 g., 78% of theory), b. p. 97—98°/10 mm., n_D^{20} 1·4161 (Adams and Adkins, *J. Amer. Chem. Soc.*, 1925, **47**, 1365, give b. p. 213°; Risseghem, *Bull. Soc. chim. Belg.*, 1919, **28**, 376, gives b. p. 105—109°/18 mm., $n_D^{17\cdot6}$ 1·4211, $n_D^{14\cdot6}$ 1·4234).

Preparation of But-1-enyl Butyl Ether.—A mixture of butaldehyde dibutyl acetal (303 g.), quinoline (5·4 g.), and *iso*propyl sulphate (0·27 g.) was passed with nitrogen (4·5 l. per hour at room temp.), at a constant rate for 4½ hours, through a nearly horizontal, empty glass tube (length 88 cm.; vol. 305 c.c.) heated over 78 cm. of its length by a furnace maintained at 350—355°. The liquid mixture was allowed to run down the entrance of the tube and was vaporised just inside the heated zone. The cooled product was collected in a flask containing quinoline (5 c.c.) and quinol (0·5 g.).

Distillation of the product from a water-bath initially at *ca.* 55 mm. and finally at 10 mm., to free it from high-boiling impurities, gave a colourless distillate (295·1 g.), and left a residue (16·2 g.) consisting partly of unchanged acetal. The main bulk of the distillate (279 g.), after the addition of quinoline (2 c.c.), was washed with successive portions (11 × 600 c.c.) of 0·5% aqueous sodium hydrogen carbonate solution; the final dried (K_2CO_3) oil (159 g.) was treated with quinol (0·15 g.) and quinoline (2 c.c.) and fractionated under reduced pressure through a 50-plate column, the distillate being collected in a number of arbitrary fractions: (i) n_D^{20} 1·4177 (9·1 g.), (ii)—(vii), inclusive, n_D^{20} 1·4179 (61·6 g.), (viii) n_D^{20} 1·4180 (5·2 g.), (ix) n_D^{20} 1·4181 (5·4 g.), (x) n_D^{20} 1·4188 (7·4 g.), (xi) n_D^{20} 1·4196 (10·3 g.), (xii)—(xvi), inclusive, n_D^{20} 1·4199 (50·4 g.).

Fractions (ii)—(vii), inclusive, were pure *cis-but-1-enyl butyl ether*, b. p. 35·5°/10·5 mm., 138·5°/751 mm. (Found: C, 75·05; H, 12·7. $C_8H_{16}O$ requires C, 74·95; H, 12·6%). A sample (504·8 mg.) in dioxan (10 c.c.) shaken in hydrogen in the presence of platinic oxide (Adams's) catalyst (50·8 mg.) absorbed 90·5 c.c. (measured at N.T.P. and corrected for absorption by the catalyst) (theoretical for $C_8H_{16}O\overline{|}$ is 88·2 c.c.).

Fractions (xii)—(xvi), inclusive, were pure trans-*but-1-enyl butyl ether*, b. p. 41·5°/10 mm., 146·5°/750 mm. (Found: C, 75·25; H, 12·55%). A sample (448·7 mg.) in dioxan (10 c.c.) shaken in hydrogen in the presence of platinic oxide (Adams's) catalyst (51·4 mg.) absorbed 77·6 c.c. (at N.T.P. and corrected for absorption by the catalyst) (theoretical for $C_8H_{16}O\overline{|}$ is 78·4 c.c.).

The isomers were comparatively stable and could be distilled unchanged at atmospheric pressure. Storage of them in glass vessels at room temperature in diffused daylight for several weeks produced no change in their refractive indices.

If the crude product from the furnace was not washed with dilute sodium hydrogen carbonate solution but was fractionated directly there were obtained (from 207 g. of crude product): (i) a constant-boiling mixture (170·5 g.), b. p. 28°/11·5 mm., n_D^{20} 1·4123, of butanol and but-1-enyl butyl ether, containing approximately 60% wt./wt. of the ether (estimated by oximation), and (ii) *trans*-but-1-enyl butyl ether (17·2 g.), b. p. 41·5°/10 mm., n_D^{20} 1·4200.

Conversion of the Isomers into Di-n-butyl Ether.—(a) *cis-Isomer.* The lower-boiling isomer (10·0 g.) was mixed with Raney nickel (*ca.* 2 g. of "paste") and a little methanol (*ca.* 2 c.c.) and shaken in an

atmosphere of hydrogen until absorption of gas ceased. The catalyst was filtered off, washed with a little methanol, and the combined filtrate and washings were shaken with very dilute sulphuric acid, then with water, and dried (Na_2SO_4), and fractionated to give di-*n*-butyl ether (8·3 g.), b. p. 139·5—140°/750 mm., n_D^{20} 1·3988. An authentic sample of this ether had b. p. 141·1° (corr.)/745 mm., n_D^{20} 1·3988.

(*b*) trans-*Isomer*. Hydrogenation of the higher-boiling isomer (10·05 g.) in a similar manner also afforded di-*n*-butyl ether (8·3 g.), b. p. 139·5—140°/750 mm., n_D^{20} 1·3988, which was shown by examination of its infra-red absorption spectrum to be identical with that obtained in (*a*).

Hydrolysis of the Isomers.—Addition of either isomer to aqueous-ethanolic sulphuric acid containing 2 : 4-dinitrophenylhydrazine gave butaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 121—122° (from ethanol). The m. p. was undepressed in each case on admixture with authentic material, m. p. 121—122°.

With aqueous-ethanolic hydrochloric acid containing *p*-nitrophenylhydrazine each isomer similarly gave butaldehyde *p*-nitrophenylhydrazone, m. p. 89—90° (from ethanol); the m. p.s were undepressed on admixture with authentic material, m. p. 89—90°.

The authors are indebted to Mr. H. C. Highet for carrying out the precise fractionation of the mixed isomers, and to the Directors of the Distillers Co., Ltd., for permission to publish this paper.

THE DISTILLERS CO., LTD., RESEARCH AND DEVELOPMENT DEPT.,
GREAT BURGH, EPSOM, SURREY. [*Received, July 18th*, 1951.]

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738. *The Synthesis and Reactions of Branched-chain Hydrocarbons. Part II.* Hydrocarbons with Two or More Quaternary Carbon Atoms.*

By E. M. GUTMAN and W. J. HICKINBOTTOM.

2 : 2 : 6 : 6-Tetramethyloctane has been prepared by the reaction of 6-chloro-2 : 2 : 6-trimethyloctane with methylmagnesium iodide. 2 : 2 : 9 : 9-Tetramethyldecane, 3 : 3 : 10 : 10-tetramethyldodecane, and 2 : 2 : 15 : 15-tetramethylhexadecane have been obtained by reaction of the appropriate Grignard reagent with silver bromide; and 2 : 2 : 6 : 10 : 10-pentamethyl- and 2 : 2 : 10 : 10-tetramethyl-6-(4 : 4-dimethylpentyl)undecane and 3 : 3 : 7 : 11 : 11-pentamethyltridecane by hydrogenation of the corresponding olefins. The structures of these olefins have been established by ozonolysis.

The investigation described in Part I * of this series has been continued with alkyl halides $R{\cdot}CMe_2{\cdot}[CH_2]_x{\cdot}CH_2Br$ (R = Me or Et; x = 2 or 5), which are readily accessible by the peroxide-catalysed addition of hydrogen bromide to olefins $R{\cdot}CMe_2{\cdot}[CH_2]_{x-1}{\cdot}CH{:}CH_2$. Three such bromides were prepared by the technique described by Hickinbottom and Porter (*J. Inst. Petr.*, 1949, **35**, 624), namely: 1-bromo-4 : 4-dimethylpentane, 1-bromo-4 : 4-dimethylhexane, and 1-bromo-7 : 7-dimethyloctane; there was no evidence of the formation of appreciable quantities of the isomeric bromides in these preparations although particular attention was paid to this since Whitmore and Homeyer (U.S.P. 2,151,252) reported that a serious proportion of 2-bromo-4 : 4-dimethylhexane was formed from 4 : 4-dimethylhex-1-ene. That the product obtained in the present work is indeed 1-bromo-4 : 4-dimethylhexane was shown by the following sequence of reactions: alkyl bromide ⟶ 4 : 4-dimethylhexan-1-ol ⟶ 3 : 3-dimethyl pentane-1-carboxylic acid. The identity of 1-bromo-7 : 7-dimethyloctane was established in a similar manner.

The Grignard compounds derived from these bromo-compounds yielded the following alcohols by reaction with suitable ketones: 3 : 7 : 7-trimethyloctan-3-ol; 3 : 7 : 7-trimethylnonan-3-ol; 2 : 2 : 6-trimethylundecan-6-ol; 3 : 10 : 10-trimethylundecan-3-ol; and 2 : 2 : 6-trimethylpentadecan-6-ol.

It was hoped that conversion of these alcohols into the corresponding chloride and then the action of methylmagnesium iodide would provide a convenient route to hydrocarbons with two quaternary carbon atoms. Experience with 6-chloro-2 : 2 : 6-trimethyloctane showed that 2 : 2 : 6 : 6-tetramethyloctane could be prepared in this way, but the yield was poor and

* Part I, *J.*, 1951, 2064.

removal of the associated olefins was tedious and made isolation of the pure hydrocarbon difficult. As this method was unsatisfactory, the reaction of our Grignard reagents with silver bromide (Gardner and Bergstrom, *J. Amer. Chem. Soc.*, 1929, **51**, 3375) was examined: 2 : 2 : 9 : 9-tetramethyldecane, 3 : 3 : 10 : 10-tetramethyldodecane, and 2 : 2 : 15 : 15-tetramethylhexadecane were thus prepared in 53—66% yield.

An alternative route to paraffins with at least two quaternary carbon atoms consists in the hydrogenation of olefins derived from alcohols formed by the reaction of our Grignard compounds with esters of carboxylic acids. From ethyl acetate, 2 : 2 : 6 : 10 : 10-pentamethylundecan-5-ol and 3 : 3 : 7 : 11 : 11-pentamethyltridecan-7-ol were prepared in good yield; 2 : 2 : 10 : 10-tetramethyl-6-(4 : 4-dimethylpentyl)undecan-6-ol was similarly obtained from ethyl 4 : 4-dimethylpentane-1-carboxylate. The dehydration of alcohols having quaternary carbon atoms may result in an alteration in the carbon skeleton to a greater or less extent. It was found that a smooth and satisfactory dehydration could be effected by refluxing them with phthalic anhydride and no evidence of rearrangement during the process could be detected on examination of the products of ozonolysis of the olefins thus formed. This method of dehydration appears to have advantages over those generally used for tertiary alcohols; it avoids the inconveniences of the Tschugaeff technique, whereas the alternative method of refluxing them with acetic anhydride and sodium acetate introduces small amounts of impurities which are difficult to remove (Hickinbottom and Sandrock, unpublished observations).

In our dehydrations it was observed that tertiary alcohols $R_2CMe{\cdot}OH$ gave only a relatively low proportion of olefins of the type $R_2C{:}CH_2$; loss of water occurred mainly in the direction of the larger groups.

Hydrogenation of the olefins in presence of Raney nickel at 100°/30—40 atmospheres gave the corresponding paraffins smoothly and in good yield.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss. M. p.s are uncorrected.)

1-Bromo-4 : 4-dimethylpentane was obtained in 85% yield by the addition of hydrogen bromide to 4 : 4-dimethylpent-1-ene in benzene containing approx. 0·2% of ascaridole (Hickinbottom and Porter, *J. Inst. Petr.*, 1949, **35**, 624): it had b. p. 56—57°/19 mm. and n_D^{20} 1·4485. Whitmore and Homeyer (*J. Amer. Chem. Soc.*, 1933, **55**, 4555) give b. p. 70—71°/35 mm., n_D^{20} 1·4484.

1-Bromo-4 : 4-dimethylhexane, prepared similarly from 4 : 4-dimethylhex-1-ene in 67% yield, had b. p. 82·5—84·2°/23 mm., n_D^{20} 1·4579—1·4582 (Found: C, 49·9; H, 8·75; Br, 41·3. Calc. for $C_8H_{17}Br$: C, 49·75; H, 8·85; Br, 41·4%). It was characterised by its mercuribromide, m. p. 97—98° (Marvel, Gauerke, and Hill, *ibid.*, 1925, **47**, 3009). There was no detectable amount of the lower-boiling 2-bromo-4 : 4-dimethylhexane which Whitmore and Homeyer (*loc. cit.*) report as one of the products of the peroxide-catalysed addition of hydrogen bromide to 4 : 4-dimethylhex-1-ene in the absence of a diluent.

1-Bromo-4 : 4-dimethylhexane in ether gives the Grignard compound in an average yield of 77%; aerial oxidation affords 4 : 4-dimethylhexan-1-ol, b. p. 95—98°/21 mm., $n_D^{20\cdot1}$ 1·4351 (68% yield), which gives a *hydrogen 3-nitrophthalate*, m. p. 181° (Found: C, 60·0; H, 6·45; N, 4·45. $C_{16}H_{21}O_6N$ requires C, 59·4; H, 6·55; N, 4·3%). Oxidation of the alcohol by dichromate and aqueous sulphuric acid gave 3 : 3-dimethylpentane-1-carboxylic acid, b. p. 139—140·5°/28 mm., $n_D^{20\cdot1}$ 1·4324 (61% yield) (Found: C, 66·6; H, 11·1. Calc. for $C_8H_{16}O_2$: C, 66·6; H, 11·2%), the *S*-benzylthiuronium salt of which has m. p. 152—153° (Campbell, Carter, and Slater, *J.*, 1947, 1745, give m. p. 150°) (Found: C, 61·4; H, 8·4; N, 9·1; S, 10·3. Calc. for $C_{18}H_{28}O_2N_2S$: C, 61·9; H, 8·4; N, 9·0; S, 10·3%); the *p-bromophenacyl* ester has m. p. 68° (Found: C, 56·65; H, 6·3. $C_{16}H_{21}O_3Br$ requires C, 56·3; H, 6·2%).

4 : 4-Dimethylhex-1-ene, used as a starting point for the preparation of 1-bromo-4 : 4-dimethylhexane was prepared in 57% yield by reaction of allyl bromide with *tert.*-amylmagnesium chloride in ether at 12—15° (Whitmore and Homeyer, *loc. cit.*; Liberman and Kazansky, *Compt. rend. Acad. Sci. Russ.*, 1943, **40**, 353).

1-*Bromo*-7 : 7-*dimethyloctane* (Found: C, 54·8; H, 9·9; Br, 36·3. $C_{10}H_{21}Br$ requires C, 54·3; H, 9·6; Br, 36·1%) was obtained in 82% yield by the addition of hydrogen bromide to 7 : 7-dimethyloct-1-ene, b. p. 96—100°/13 mm., $n_D^{20\cdot1}$ 1·4549—1·4550. It formed the alkylmagnesium bromide (in 90% yield), which by aerial oxidation gave 7 : 7-dimethyloctan-1-ol (56%), b. p. 103—104°/15 mm., n_D^{19} 1·4384 [*hydrogen 3-nitrophthalate*, m. p. 166° (Found: C, 61·5; H, 7·1; N, 4·4. $C_{18}H_{25}O_6N$ requires C, 61·5; H, 7·2; N, 4·0%)]. Oxidation of the alcohol (5·3 g.) by dichromate and aqueous sulphuric acid gave 6 : 6-*dimethylheptane*-1-*carboxylic acid*, b. p. 138—139°/9 mm., n_D^{20} 1·4338 (2·8 g.) (Found: C, 69·5; H, 11·65. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%), which affords a *p-phenylphenacyl* ester, m. p. 80° (Found: C, 78·1; H, 8·2. $C_{34}H_{40}O_3$ requires C, 78·6; H, 8·25%), and a *p*-bromophenacyl ester, m. p. 82°.

7 : 7-*Dimethyloct*-1-*ene*, obtained in 80% yield by the reaction of allyl bromide (88 g.) with the Grignard compound from 1-bromo-4 : 4-dimethylpentane (161 g.), had b. p. 152—152·5°, n_D^{20} 1·4183 (Found: C, 85·8; H, 14·0. $C_{10}H_{20}$ requires C, 85·6; H, 14·4%). Ozonolysis in chloroform gave formaldehyde (dimedone derivative, m. p. and mixed m. p. 190°) and 5 : 5-dimethylhexane-1-carboxylic

acid, b. p. 128—130°/11 mm., $n_D^{20\cdot3}$ 1·4300 (*p*-phenylphenacyl ester, m. p. and mixed m. p. 89°). A specimen of this acid prepared from 1-bromo-4 : 4-dimethylpentane by reaction with malonic ester boiled at 129—130°/13 mm., had $n_D^{20\cdot1}$ 1·4298 (Found : C, 68·7; H, 11·6. Calc. for $C_9H_{18}O_2$: C, 68·3; H, 11·5%) (Whitmore *et al.*, U.S.P., 2,032,159, give b. p. 145°/20 mm.), and gave a p-*phenylphenacyl* ester, m. p. 89° (Found : C, 78·3; H, 8·0. $C_{23}H_{28}O_3$ requires C, 78·4; H, 8·0%).

Preparation of 2 : 2 : 6 : 6-*Tetramethyloctane*.—2 : 2 : 6 : 6-Tetramethyloctane was obtained in poor yield by reaction of methylmagnesium iodide with 6-chloro-2 : 2 : 6-trimethyloctane.

(a) 6-*Chloro*-2 : 2 : 6-*trimethyloctane*. The Grignard compound from 1-bromo-4 : 4-dimethylpentane (190·5 g.) and ethyl methyl ketone (64 g.) gave 3 : 7 : 7-*trimethyloctan*-3-*ol* (134 g.), b. p. 101—103°/21 mm., $n_D^{20\cdot7}$ 1·4339 (Found : C, 77·0; H, 14·1. $C_{11}H_{24}O$ requires C, 76·7; H, 14·0%). Saturation of the alcohol (57 g.) with dry hydrogen chloride at 0° gave a dark red upper layer, which was separated and washed successively with ice-cold sodium hydrogen carbonate solution and ice-water. It was freed from the last traces of hydrogen chloride by storage for 24 hours in a vacuum-desiccator containing sodium hydroxide. Pure 6-*chloro*-2 : 2 : 6-*trimethyloctane* (yield, 57 g.) is a colourless liquid with a pleasant odour, becoming yellow on prolonged storage; it has b. p. 48·8—49·3°/0·7 mm., $n_D^{20\cdot3}$ 1·4365 (Found : C, 69·5; H, 11·9; Cl, 18·3. $C_{11}H_{23}Cl$ requires C, 69·25; H, 12·15; Cl, 18·6%).

(b) *Reaction of* 6-*chloro*-2 : 2 : 6-*trimethyloctane with methylmagnesium iodide*. The foregoing chloride (50 g.) was added dropwise, with stirring, to a boiling filtered ethereal solution of methylmagnesium iodide (0·31 g.-mol.). A greenish-white lower layer separated. Heating and stirring were continued for 2 days. The product was isolated by adding ice and ammonium sulphate solution and distilling the dried ethereal solution through an efficient column. The following fractions were obtained : (*a*) b. p. 23—59°/17 mm. (0·4 g.), (*b*) b. p. 59—67°/17 mm. (4·4 g.), (*c*) b. p. 68—72·5°/17 mm. (34 g.), and (*d*) b. p. above 73°/17 mm. (2 g.). Fraction (*c*), obviously a mixture, was refluxed over sodium for 3 hours and then shaken with ten successive portions of 80% sulphuric acid till the bulk of the unsaturated hydrocarbon had been removed. Systematic fractionation through a 6″ column (10—15 theoretical plates) concentrated 2 : 2 : 6 : 6-*tetramethyloctane* into the fraction, b. p. 182·2—183·3°. It still contained some olefin; this was removed by percolation through a column packed with silica gel till the refractive index was not further altered (n_D^{20} 1·4203) (Found : C, 84·5; H, 15·05. $C_{12}H_{26}$ requires C, 84·6; H, 15·4%).

The following alcohols were prepared by reaction of the appropriate alkylmagnesium bromide with the appropriate ketone :

3 : 7 : 7-*Trimethylnonan*-3-*ol*, b. p. 62—73°/0·6 mm., $n_D^{19\cdot8}$ 1·4431 (yield 77%) (Found : C, 77·0; H, 13·9. $C_{12}H_{26}O$ requires C, 77·4; H, 14·1%).

2 : 2 : 6-*Trimethylundecan*-6-*ol*, b. p. 126—128°/11 mm., n_D^{20} 1·4418 (yield 67%) (Found : C, 78·6; H, 14·3. $C_{14}H_{30}O$ requires C, 78·4; H, 14·1%).

3 : 10 : 10-*Trimethylundecan*-3-*ol*, b. p. 97°/0·8 mm., $n_D^{20\cdot3}$ 1·4437 (yield 68%) (Found : C, 78·2; H, 13·8. $C_{14}H_{30}O$ requires C, 78·4; H, 14·1%).

2 : 2 : 6-*Trimethylpentadecan*-6-*ol*, b. p. 136—137°/0·5 mm., n_D^{20} 1·4480 (yield 66%) (Found : C, 80·4; H, 14·2. $C_{18}H_{38}O$ requires C, 80·0; H, 14·2%).

Preparation of Paraffins with Two Quaternary Carbon Atoms by the Gardner–Bergstrom Reaction.—(a) 2 : 2 : 9 : 9-*Tetramethyldecane*. The filtered Grignard compound from 1-bromo-4 : 4-dimethylpentane (0·125 g.-mol.) was treated in ice-cold ether with dry silver bromide with constant stirring. The reaction was completed by 1 hour's heating under reflux. 2 : 2 : 9 : 9-*Tetramethyldecane* was isolated by distillation of the filtered reaction mixture, drying, and then shaking it successively with several small volumes of sulphuric acid. The product distilled over sodium at 93°/10 mm. and had n_D^{20} 1·4250 (Found : C, 85·15; H, 15·2. $C_{14}H_{30}$ requires C, 84·75; H, 15·25%).

(b) 3 : 3 : 10 : 10-*Tetramethyldodecane*. This *hydrocarbon*, b. p. 127°/10 mm., n_D^{20} 1·4388 (Found : C, 85·0; H, 15·3. $C_{16}H_{34}$ requires C, 84·9; H, 15·1%), was similarly prepared.

(c) 2 : 2 : 15 : 15-*Tetramethylhexadecane*. This *compound* had b. p. 134°/0·4 mm., n_D^{20} 1·4401 (Found : C, 85·5; H, 14·85. $C_{20}H_{42}$ requires C, 85·0; H, 15·0%).

Preparation of Paraffins with Two or Three Quaternary Carbon Atoms from the Corresponding Alcohols.—(a) 2 : 2 : 6 : 10 : 10-*Pentamethylundecane*. The Grignard compound from 1-bromo-4 : 4-dimethylpentane (0·8 g.-mol.) reacted with an ethereal solution of ethyl acetate (0·32 g.-mol.), to give 2 : 2 : 6 : 10 : 10-*pentamethylundecan*-6-*ol*, b. p. 122—124°/4 mm., m. p. 64·5 [from light petroleum (b. p. 40—60°)] (54 g.) (Found : C, 79·1; H, 14·1. $C_{16}H_{34}O$ requires C, 79·3; H, 14·1%).

Dehydration of the alcohol (50·5 g.) was effected by heating it at 180° for 3 hours with an equimolecular proportion of phthalic anhydride in a flask fitted with a reflux condenser and an adjustable take-off to remove the water as it was formed. The resulting olefin was refluxed over sodium before fractionation and then had b. p. 122—127°/19 mm., n_D^{20} 1·4408—1·4410 (yield, 35 g.) (Found : C, 85·8; H, 14·3. $C_{16}H_{32}$ requires C, 85·6; H, 14·4%). Ozonolysis of a portion (15 g.) gave formaldehyde (dimedone derivative, m. p. and mixed m. p. 190°), 6 : 6-dimethylheptan-2-one (8·5 g.), $n_D^{20\cdot4}$ 1·4188—1·4232 (semicarbazone, m. p. and mixed m. p. 180—181°), 2 : 2 : 10 : 10-tetramethylundecane-6-one (0·3 g.), $n_D^{20\cdot4}$ 1·4320 (semicarbazone, m. p. and mixed m. p. 131°), and *neo*pentylacetic acid, b. p. 121°/29 mm., $n_D^{20\cdot1}$ 1·4201 (6·3 g.) [amide, m. p. and mixed m. p. 139—140° (Whitmore and Homeyer, *J. Amer. Chem. Soc.*, 1933, **55**, 4555); *S*-benzylthiuronium salt, m. p. and mixed m. p. 154·5°]. The olefin thus consists essentially of 2 : 2 : 6 : 10 : 10-*pentamethylundec*-5-*ene* with a small proportion of 6 : 6-*dimethyl*-2-(4 : 4-*dimethylpentyl*)*hept*-1-*ene*.

Hydrogenation of the olefin (Raney nickel; ethyl alcohol; 100°/30 atms.) gave 2 : 2 : 6 : 10 : 10-*pentamethylundecane*, b. p. 80·5°/0·5 mm., n_D^{20} 1·4299 (76%) (Found : C, 85·15; H, 15·05. $C_{16}H_{34}$ requires C, 84·9; H, 15·1%).

(b) **3 : 3 : 7 : 11 : 11-*Pentamethyltridecane*.** The Grignard compound from 1-bromo-4 : 4-dimethylhexane (0·4 g.-mol.), and ethyl acetate (0·17 g.-mol.) gave some low-boiling material (7·5 g.) and **3 : 3 : 7 : 11 : 11-*pentamethyltridecan*-7-*ol***, m. p. 39·5°, b. p. 126—126·5°/1·8 mm. (32 g.) (Found: C, 79·8; H, 14·4. $C_{18}H_{38}O$ requires C, 79·9; H, 14·2%).

This was dehydrated with phthalic anhydride at 180° to give an olefin, b. p. 146—148°/10 mm., $n_D^{20\cdot4}$ 1·4515—1·4519 (Found: C, 85·7; H, 14·4. $C_{18}H_{36}$ requires C, 85·6; H, 14·4%), consisting largely of **3 : 3 : 7 : 11 : 11-*pentamethyltridec*-6-*ene*** with a little **6 : 6-dimethyl-2-(4 : 4-dimethylhexyl)oct-1-ene**. It gave, on ozonolysis, formaldehyde (dimedone derivative, m. p. and mixed m. p. 189°), **6 : 6-dimethyloctan-2-one** (semicarbazone, m. p. and mixed m. p. 143·5—144·5°; cf. below), and **3 : 3-dimethylpentane-1-carboxylic acid** (*S*-benzylthiuronium salt, m. p. and mixed m. p. 152°); a small fraction corresponding to **3 : 3 : 11 : 11-tetramethyltridecan-7-one** was obtained but it could not be purified sufficiently for exact characterisation.

Hydrogenation of the olefin (Raney nickel; ethyl alcohol; 100°/40 atms.; 4 hours) gave **3 : 3 : 7 : 11 : 11-*pentamethyltridecane*** (65%), b. p. 101°/0·35 mm., n_D^{20} 1·4419, d_{25}^{15} 0·7911 (Found: C, 84·6; H, 14·95. $C_{18}H_{38}$ requires C, 84·95; H, 15·05%).

(c) **2 : 2 : 10 : 10-*Tetramethyl*-6-(4 : 4-*dimethylpentyl*)*undecane***. The Grignard compound from 1-bromo-4 : 4-dimethylpentane (0·15 g.-mol.) and ethyl **4 : 4-dimethylpentane-1-carboxylate** (0·06 g.-mol.) gave **2 : 2 : 10 : 10-*tetramethyl*-6-(4 : 4-*dimethylpentyl*)*undecan*-6-*ol*** (57%), m. p. 48°, b. p. 140·5°/0·8 mm. (Found: C, 81·25; H, 14·45. $C_{23}H_{46}O$ requires C, 80·9; H, 14·2%). Heating the alcohol with iodine caused dehydration to **2 : 2 : 10 : 10-*tetramethyl*-6-(4 : 4-*dimethylpentyl*)*undec*-5-*ene*** (77%), b. p. 112—113°/0·6 mm., n_D^{20} 1·4464 (Found: C, 85·8; H, 14·45. $C_{23}H_{44}$ requires C, 85·6; H, 14·4%). Ozonolysis in chloroform gave **2 : 2 : 10 : 10-tetramethylundecan-6-one** (semicarbazone, m. p. and mixed m. p. 131·5—132·5°) and *neo*pentylacetic acid (amide, m. p. and mixed m. p. 138—139°). Hydrogenation of the olefin (Raney nickel; ethyl alcohol; 104—140°/75 atms.) gave **2 : 2 : 10 : 10-*tetramethyl*-6-(4 : 4-*dimethylpentyl*)*undecane*** (80%), b. p. 121°/0·4 mm., n_D^{20} 1·4414, d_{20}^{20} 0·7882 (Found: C, 85·45; H, 14·6. $C_{23}H_{48}$ requires C, 85·1; H, 14·9%).

For the identification of the products of the ozonolysis of the olefins described above, the following reference compounds were prepared.

1-*Cyano*-4 : 4-*dimethylpentane*, b. p. 88—89°/24 mm., $n_D^{20\cdot1}$ 1·4194 (Found: C, 76·6; H, 11·8; N, 11·2. $C_8H_{15}N$ requires C, 76·7; H, 12·1; N, 11·2%), was obtained in 74% yield by the reaction of 1-bromo-4 : 4-dimethylpentane with aqueous-alcoholic potassium cyanide. With methylmagnesium iodide it yielded **6 : 6-*dimethylheptan*-2-*one***, b. p. 78—79°/22 mm., n_D^{16} 1·4225 (Found: C, 75·5; H, 12·3. $C_9H_{18}O$ requires C, 76·1; H, 12·7%) [**2 : 4-*dinitrophenylhydrazone***, m. p. 107—108° (Found: C, 56·0; H, 6·6. $C_{15}H_{22}O_4N_4$ requires C, 55·9; H, 6·9%)]. Hydrolysis of the nitrile gave **4 : 4-dimethylpentane-1-carboxylic acid** (84%), b. p. 126—129°/21 mm., m. p. 39° (Found: C, 67·1; H, 10·8. Calc. for $C_8H_{16}O_2$: C, 66·7; H, 11·1%) (Whitmore *et al.*, U.S.P., 2,032,159, give b. p. 130°/20 mm., m. p. 38°) [***amide***, m. p. 97—98° (Found: N, 9·6. $C_8H_{17}ON$ requires N, 9·8%)]. The chloride, b. p. 79—82°/22 mm., obtained from the acid in 79% yield by the action of thionyl chloride, reacted in benzene solution with di-(4 : 4-dimethylpentyl)cadmium to give **2 : 2 : 10 : 10-*tetramethylundecan*-6-*one*** (51%), b. p. 132°/10 mm., $n_D^{20\cdot1}$ 1·4353 (Found: C, 79·4; H, 13·2. $C_{15}H_{30}O$ requires, C, 79·6; H, 13·4%) [***semicarbazone***, m. p. 131·5—132·5° (Found: C, 680; H, 11·6; N, 14·8. $C_{16}H_{33}ON_3$ requires C, 67·8; H, 11·7; N, 14·8%)].

Di-(4 : 4-dimethylhexyl)cadmium and acetyl chloride in benzene gave **6 : 6-*dimethyloctan*-2-*one***, which was purified through its ***semicarbazone***, m. p. 145—146° (Found: C, 62·4; H, 10·9. $C_{11}H_{23}ON_3$ requires C, 61·9; H, 10·9%). The pure ketone had b. p. 96°/33 mm., $n_D^{20\cdot1}$ 1·4289 (Found: C, 77·1; H, 13·0. $C_{10}H_{20}O$ requires C, 76·9; H, 12·9%).

3 : 3 : 11 : 11-Tetramethyltridecan-7-one, b. p. 114—115°/0·4 mm., $n_D^{19\cdot3}$ 1·4488, was prepared in 54% yield by reaction of di-(4 : 4-dimethylhexyl)cadmium and **4 : 4-dimethylhexane-1-carboxyl chloride**. It was characterised by its ***semicarbazone***, m. p. 108° (Found: C, 6902; H, 11·8; N, 13·3. $C_{18}H_{37}ON_3$ requires C, 69·4; H, 12·0; N, 13·5%). **4 : 4-*Dimethylhexane*-1-*carboxylic acid***, required for this preparation, was obtained by the alkaline hydrolysis of 1-cyano-4 : 4-dimethylhexane. The free acid had b. p. 128·5—130°/9 mm., $n_D^{20\cdot1}$ 1·4362 (Found: C, 68·4; H, 11·3. $C_9H_{18}O_2$ requires C, 68·3; H, 11·5%), and gave a *S*-benzylthiuronium salt, m. p. 146°, and an acid chloride, b. p. 82—84°/10·5 mm., n_D^{20} 1·4423. **1-*Cyano*-4 : 4-*dimethylhexane*** was prepared in 76% yield by the reaction of 1-bromo-4 : 4-dimethylhexane with potassium cyanide in aqueous-alcoholic solution; it had b. p. 88—90°/10 mm., $n_D^{20\cdot3}$ 1·4298 (Found: C, 77·7; H, 12·35; N, 10·4. $C_9H_{17}N$ requires C, 77·6; H, 12·3; N, 10·1%).

The authors thank the Institute of Petroleum for financial support and for a Scholarship to one of them (E. M. G.).

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739. *The Rate of Dehydration of Chrome Alum.*

By M. M. T. Anous, R. S. Bradley, and (the late) J. Colvin.

The rate of dehydration *in vacuo* of large single crystals of chrome alum of mass *ca.* 1 g. has been studied at thermostat temperatures of 15—35°, a McBain balance being used and special attention being paid to the self-cooling of the crystals. The activation energy is *ca.* 23 kcals. per mole, and the kinetics of dehydration are in rough agreement with the Polanyi–Wigner expression. Pressures of air up to 1 mm. of mercury scarcely affect the rate of dehydration if this is corrected to a uniform temperature to allow for self-cooling; water vapour depresses the reaction at all pressures studied up to 1·7 mm. of mercury. The dehydration has also been studied at −1·7° to −12°, at which self-cooling is negligible, a silica microbalance being used by means of which velocities of propagation of the interface as low as 0·2 Å sec.$^{-1}$ could be measured. At the low temperatures the activation energy is *ca.* 30 kcals. per mole, and the temperature-independent factor is too large in comparison with the Polanyi–Wigner theoretical value by a factor of 10^{10}. The heat of decomposition per mole of water lost for the reaction

$K_2SO_4,Cr_2(SO_4)_3,24H_2O$ (s.) ⟶ $K_2SO_4,Cr_2(SO_4)_3,12H_2O$ (s.) + $12H_2O$ (g.)

has been determined at 25° to be $\Delta H_{298} = 12{\cdot}79$ kcals.

The rate of dehydration of chrome alum *in vacuo* and in the presence of water vapour has been studied by Cooper and Garner (*Proc. Roy. Soc.*, 1940, **174**, *A*, 487) and shows some anomalous features. The activation energy for dehydration *in vacuo* was found to be of the order 31 kcals. per mole; this is much greater than the heat of dissociation (10 kcals. per mole), which is the normal activation energy for the dehydration of hydrates. The temperature-independent factor B in the expression, linear rate of propagation of the interface, $u = Be^{-E/RT}$, where E is the activation energy, is correspondingly very high in comparison with the value deduced by simple theory. The reaction was studied on isolated crystals *in vacuo*, and a large self-cooling occurred, so it seemed worth while to reinvestigate the reaction (*a*) at 15—35°, with particular attention to the measurement of the self-cooling, and (*b*) at temperatures below 0° at which self-cooling is negligible. The second method involved new techniques which are described below.

Experimental.

Dehydration 15—35° in vacuo.—A saturated solution of "AnalaR" chrome alum, prepared at a temperature not exceeding 30°, was filtered and freed from dissolved air by suction, and allowed to crystallize in a dust-free air thermostat at 20°, calcium chloride being used as absorbent. Crystals were turned over periodically, and after growth were dipped in distilled water, dried on filter-paper, and stored over powdered chrome alum in a desiccator. Owing to the influence of the vessel, the crystals had two broad parallel faces with six side faces, all faces being 111; in Fig. 1 the relation of the crystal form to the bipyramid is shown. No difference in behaviour was observed when crystallization was carried out in the presence of dilute sulphuric acid.

The dimensions of the crystals were determined by using a Vickers projection microscope and a micrometer; the weight of the crystal as calculated from the density and volume agreed with the observed weight to within a few units %. The density was found from flotation measurements with benzene to be 1·819 at 15°.

The crystal was nucleated on all faces by rubbing it with a mixture of fine carborundum and dehydrated chrome alum, and was suspended by means of a helical silica spring *A*, Fig. 2 (sensitivity 1 g. ≡ 10 mm.), so that deflection–time curves could be obtained for the loss of water *in vacuo*. From the percentage loss of weight, w, the rate of propagation of the interface, u, could be found from the geometry of the crystal, the velocity being assumed to be independent of direction. At the end of the reaction, a half of the initial water content is lost, the remainder being presumably co-ordinated to chromium. The zero time and the value of u can best be found by plotting a theoretical curve of w against ut, where t is the time, and comparing this with the experimental curve of w against $t_{obs.}$. For the same value of w we have ut and $t_{obs.}$, and hence we can plot ut against $t_{obs.}$ for various values of w. Since $ut = u(t_{obs.} - t_0)$, where t_0 is a constant, the graph of ut against $t_{obs.}$ should be rectilinear, and from this graph we can determine u from the slope and t_0 from the intercept; u is found to be independent of the percentage decomposition, which shows that there is no impedance of the reaction due to the slow diffusion of water vapour through the pseudomorph.

Crystal temperatures were measured by means of a thin-junctioned copper–constantan thermocouple which was led out of the vessel *B* (Fig. 2). The broad faces of two crystals were cemented together

by means of "Durofix," in which the thermocouple was embedded with a considerable length of wire between the crystals. After the cement had dried, the pair of crystals was nucleated, suspended in the vessel *B*, and subjected to the same conditions as the crystal in *A*. The pair of crystals in *B* together equalled in weight as nearly as possible the single crystal in *A*. The thermoelectric e.m.f. was measured continuously by means of a Kent recorder, and after an initial variation in general assumed a fairly steady value during the course of the experiment. In Fig. 3 is shown the variation in temperature recorded for a crystal pair of 1·2 g., being dehydrated *in vacuo* in a thermostat at 25°.

FIG. 1.

Crystal of chrome alum and its relation to the bipyramid.

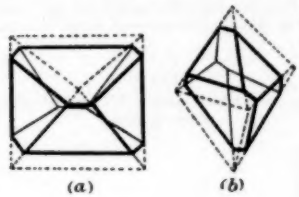
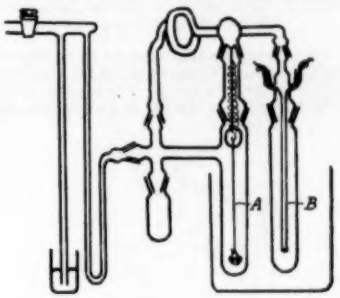


FIG. 2.

Apparatus for "high"-temperature experiments.



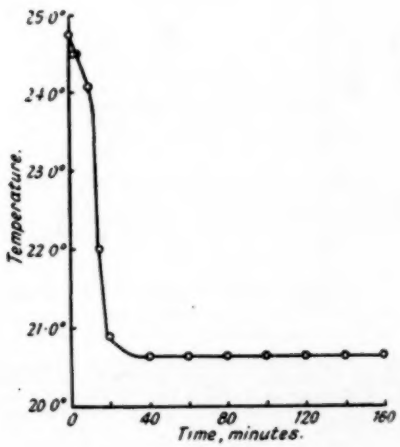


FIG. 3.

Cooling of a crystal pair of 1·2 g. weight. Temperature of bath 25°.

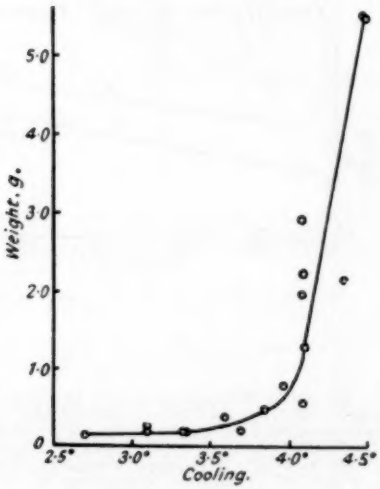


FIG. 4.

Change of cooling with weight. Temperature of bath 25°.

Values of the self-cooling for vacuum-dehydration were found at first to be considerably less than those recorded by Cooper and Garner (*loc. cit.*), and this result was confirmed when the thermocouple was inserted in a hole drilled in the crystal in an effort to record the interface temperature: owing to the brittle nature of the crystals and the short length of thermocouple wires embedded in the drilled hole, this method was not generally adopted. This discrepancy with published data was traced to the influence of the size of the crystal on self-cooling, and it was found that the self-cooling increased with increase in size of the crystal, but that for crystals above 1 g. in weight the self-cooling increases only slightly with increasing size of crystal, as shown in Fig. 4; moreover, the temperature was steadier for the large crystals (with only a slight increase in temperature as the reaction proceeded). It may be noted that a steady thermocouple temperature at the centre implies a state of uniform temperature in the crystal and a balance between the heat gained by radiation and conduction down the silica and

that lost by reaction; conduction *within* the crystal does not enter into consideration in this steady state. In our experiments the steady state was very nearly achieved (Fig. 3), but it is possible that the temperature was roughly constant because of a balancing of conductivity effects and change in heat absorbed by the reaction as the interfacial surface decreases with time. It was therefore decided to confine the work to large crystals weighing more than 1 g. The self-cooling increased considerably with increase in the thermostat temperature, owing to the increased velocity of reaction, and was slightly dependent on the percentage decomposition, as is seen from Fig. 5, which gives the self-cooling for crystal pairs weighing 1—1·5 g., undergoing dehydration *in vacuo* in a bath at 35° for 20—60% and 40—60% decomposition. The mean self-cooling for 20—60% decomposition is as follows for large crystals (the pair, 1—1·2 g. in weight).

Bath temp.	17·5°	25°	30°	35°
Self-cooling	2·15°	4·03°	6·30°	8·78°

We believe this technique to be an improvement on that previously published, for it is to be inferred from Cooper and Garner's work that the crystal pair used to measure the self-cooling did not together equal in weight the single crystal used for kinetic measurements, but were somewhat larger (confirmed by Professor W. E. Garner in private correspondence).

FIG. 5.

Change of cooling with weight. Temperature of bath 35°.

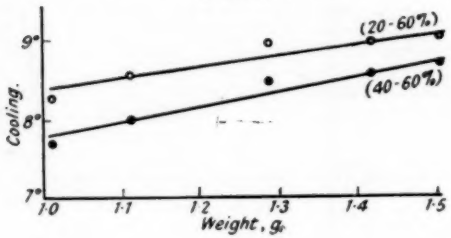
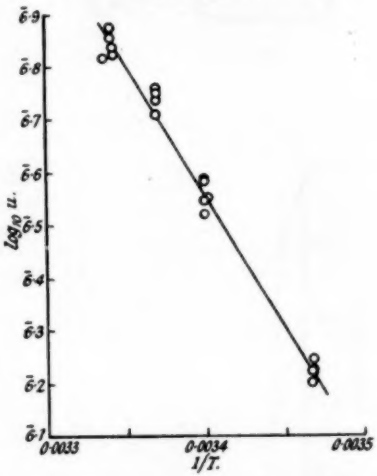


FIG. 6.

$\log_{10} u$ *plotted against* 1/T *for* 20—60% *decomposition.*



The values of $\log_{10} u$ are plotted against $1/T$, where T is the absolute temperature of the crystal, in Fig. 6. Five crystals were studied for each temperature. Activation energies of 22,800 and 22,350 cals. per mole are obtained for 20—60% and 40—60% decomposition, respectively. These values are considerably less than those obtained by Cooper and Garner, but are still much greater than the heat of the reaction. The mean temperature-independent factor $B = 3{\cdot}6 \times 10^6$, as calculated from $u = Be^{-E/RT}$ by using the experimental value of E. The values of u (in cm. sec.$^{-1}$) are shown below.

Mean linear velocity of propagation of interface.

Temp. of crystal	10^6u	Temp. of crystal	10^6u	Temp. of crystal	10^6u	Temp. of crystal	10^6u	Temp. of crystal	10^6u
				20—60% Decomposition.					
15·40°	1·57	15·33°	1·74	21·00°	3·83	23·70°	5·07	26·25°	7·49
15·40	1·65	20·98	3·49	20·97	3·29	23·70	5·63	26·50	6·51
15·34	1·64	21·00	3·79	23·70	5·59	23·70	5·39	26·00	6·62
15·28	1·66	20·90	3·54	23·70	5·67	26·25	7·12	26·08	6·85
				40—60% Decomposition.					
15·31	1·58	15·16	1·74	21·10	3·84	24·03	5·05	26·75	7·45
15·30	1·65	21·06	3·48	21·05	3·27	24·03	5·63	27·10	6·53
15·19	1·65	21·04	3·78	24·03	5·61	24·03	5·35	26·35	6·67
15·06	1·65	20·99	3·50	24·03	5·64	26·75	7·18	26·50	6·98

The pseudomorph product was pink, but the outer layer was greenish to bluish-grey, a phenomenon observed with mixed chromium and aluminium potassium alums by Acock, Garner, Milsted, and Willavoys (*Proc. Roy. Soc.*, 1947, **189**, *A*, 508). The water content of each layer was determined by means of a micro-technique by heating at 300—350° to constant weight, and appeared to be the same. This identity was confirmed by *X*-ray examination of the powders, kindly undertaken by Mr. P. Markey, of this Department. In addition, $Cr_2(SO_4)_3,12H_2O$ was prepared by dehydration of violet $Cr_2(SO_4)_3,18H_2O$ *in vacuo*, and when it was mixed with potassium sulphate in molecular proportions it gave an *X*-ray powder photograph which differed considerably from that given by the two layers, suggesting that the result of the dehydration was not a mixture of separate crystals of K_2SO_4 and $Cr_2(SO_4)_3,12H_2O$, but a solid solution not yet prepared in the form of large crystals. An attempt to prepare the double salt was made by crystallizing a solution of chrome alum in a concentrated solution of sulphuric acid; green crystals were obtained, and were washed with benzene and alcohol and dried. The *X*-ray powder photograph differed slightly from that of the pseudomorph.

FIG. 7.

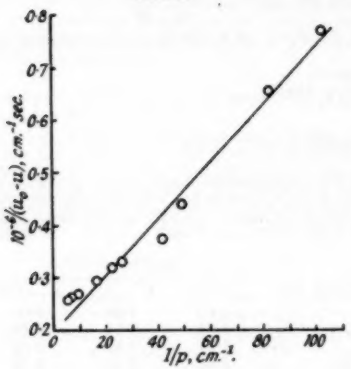
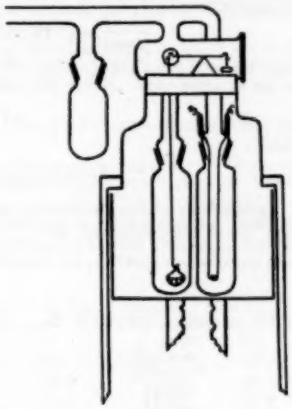


FIG. 8.

Apparatus for low-temperature experiments.



Effect of Air and of Water Vapour on the Rate of Dehydration.—The experiments described above were repeated at a bath temperature of 25° in the presence of air up to a pressure of 10^{-1} cm. of mercury, with very little influence on the rate after allowance for the self-cooling, except for a shallow maximum, as shown by the following data corrected to a crystal temperature of 25°:

Pressure, cm. of Hg	$1{\cdot}34 \times 10^{-4}$	$1{\cdot}63 \times 10^{-3}$	$5{\cdot}63 \times 10^{-3}$	$1{\cdot}46 \times 10^{-2}$	$8{\cdot}84 \times 10^{-2}$	$1{\cdot}06 \times 10^{-1}$
$10^6 u$ (cm. sec.$^{-1}$) ...	6·36	6·42	7·68	7·62	6·79	6·19

These results suggest that the rate of loss of water is not controlled by a diffusion process through channels in the pseudomorph, since air at 1 mm. pressure would make such a process considerably slower.

The rate of dehydration was also studied at a bath temperature of 25° in the presence of water vapour at low pressures provided by a sample of water cooled by acetone and solid carbon dioxide, the temperature of which was recorded by means of a sulphur dioxide vapour-pressure thermometer. Results are given in Table I; crystals of mass 1·2 g. were used, and there is a small scatter inevitable when dealing with different crystals (see below). It will be seen that when the results are corrected

TABLE I.

Press. of H_2O vapour, cm. Hg	Self-cooling	$10^6 u$ (uncorr.), cm. sec.$^{-1}$	$10^6 u$ (corr.), cm. sec.$^{-1}$	Press. of H_2O vapour, cm. Hg	Self-cooling	$10^6 u$ (uncorr.), cm. sec.$^{-1}$	$10^6 u$ (corr.), cm. sec.$^{-1}$
0·0	4·03°	3·59	6·03	0·0761	1·50°	2·21	1·66
0·00966	2·67	3·31	4·73	0·1219	0·31	1·64	1·70
0·02375	2·02	2·61	3·36	0·1691	0·87	1·89	2·12
0·0439	1·42	2·42	2·88				

to 25° there is no trace of the maximum for rate as a function of pressure reported by Cooper and Garner from their experiments on the rate of growth of *nuclei*. The normal decrease in rate due to a back pressure of water vapour is observed as with the dehydration of $CuSO_4,5H_2O$. It is possible that the water vapour acts as a depressant by forming an adsorbed layer just above the reaction zone and thereby favouring the reverse reaction, since the reaction is reversible in the region of the interfacial reaction zone. On applying Langmuir's adsorption isotherm it would be expected that $u = u_0 - k_2 p/(k_3 + p)$,

where u_0 is the velocity when the pressure $p = 0$, or $u_0 - u = k_2 p/(k_2 + p)$. Hence $1/(u_0 - u)$ should be a linear function of $1/p$, as is found (see Fig. 7) to be very nearly true from the data of Table I (cf. Acock, Garner, Milsted, and Willavoys, *loc. cit.*).

The values of the self-cooling observed with water vapour were compared with theoretical predictions, the kinetic theory being used in a manner similar to that used by Birks and Bradley (*Proc. Roy. Soc.*, 1949, **198**, *A*, 226) but with an additional term to allow for radiation owing to the high values of the self-cooling. Cooper and Garner discussed only the latter term. The loss of heat per second due to reaction is $-(dm/dt)\Delta H/M$, where $-(dm/dt)$ is the rate of loss of mass, ΔH the reaction heat per mole of water lost, and M the molecular weight of water. The gain of heat in ergs per second is $5{\cdot}735 \times 10^{-5} A(T_1^4 - T_0^4)$ from radiation, where T_1 is the temperature of the thermostat and T_0 that of the crystal and A is the crystal area, and $2k(T_1 - T_0)\alpha A p/\sqrt{2\pi m k T_1}$ from molecular bombardment, where p is the gas pressure, α the thermal accommodation coefficient, and m the mass of a water molecule. Hence, at thermal equilibrium, if ΔH is expressed in ergs per mole

$$\frac{p}{(2\pi m k T_1)^{\frac{1}{2}}} \cdot 2k(T_1 - T_0)\alpha A + 5{\cdot}735 \times 10^{-5} A(T_1^4 - T_0^4) = -\frac{dm}{dt} \cdot \frac{\Delta H}{M}$$

or, approximately,

$$\frac{p}{(2\pi m k T_1)^{\frac{1}{2}}} \cdot 2k \cdot \Delta T \cdot \alpha A + 5{\cdot}735 \times 10^{-5} A \Delta T \cdot 4T_1^3 = -\frac{dm}{dt} \cdot \frac{\Delta H}{M}$$

since $\Delta T = T_1 - T_0 \ll T_1$ or T_0. The approximation $T_1^4 - T_0^4 = 4T_1^3 \cdot \Delta T$ is in error to only 3% in the extreme case. Hence the self-cooling

$$\Delta T = -\frac{dm}{dt} \cdot \frac{\Delta H}{M} \cdot \frac{1}{\theta_1 + \theta_2} \text{ (app.)},$$

where

$$\theta_1 = \frac{p}{(2\pi m k T_1)^{\frac{1}{2}}} \cdot 2k\alpha A, \text{ and } \theta_2 = 5{\cdot}735 \times 10^{-5} \cdot 4T_1^3 A$$

Calculations of the theoretical value of ΔT by using the experimental mean values of dm/dt for 20—60% decomposition for crystals of area approximately 5 cm.^{2} for $\alpha = 0{\cdot}3$, 0·5, and 1·0, are made and are compared with the experimental results in the following table. It will be seen that, apart from experimental scatter, the experimental results are in reasonable accord with $\alpha = 1{\cdot}0$. It should

Press. of water vapour, cm. Hg	Experimental self-cooling, ΔT	Theoretical ΔT : $\alpha = 1{\cdot}0$	$\alpha = 0{\cdot}5$	$\alpha = 0{\cdot}3$
0·0	4·03°	4·00	4·00	4·00
0·00966	2·67	3·02	3·11	3·15
0·02575	2·02	2·31	2·50	2·59
0·0439	1·42	2·61	2·95	3·12
0·0761	1·50°	1·66	2·00	2·19
0·1219	0·31	1·06	1·42	1·64
0·1691	0·87	0·93	1·28	1·50

be noted that black-body radiation and no conduction by the silica fibre are assumed, and that a condition of thermal equilibrium is assumed.

Rate of Dehydration at Low Temperatures.—Since the self-cooling ΔT decreases as the thermostat temperature decreases ($\log_{10} \Delta T$ is a linear function of T), the self-cooling at temperatures less than 0° should be negligible, and this should provide an ideal method of studying solid reactions. Owing, however, to the low velocities at low temperatures a much more refined apparatus is necessary, and we have used the microbalance and technique described by one of us and others (Bradley, Evans, and Whytlaw-Gray, *Proc. Roy. Soc.*, 1946, *A*, **286**; Birks and Bradley, *ibid.*, 1949, *A*, **198**, 226; Bradley and Shellard, *ibid.*, p. 239; Bradley, *ibid.*, 1951, *A*, **205**, 553; Bradley and Waghorn, *ibid.*, 1951, *A*, **206**, 65). We have succeeded in making accurate measurements on velocities as low as 0·2 Å per second; much lower linear speeds could be measured if necessary.

The silica microbalance had a sensitivity of 107·1 μg. per mm., and the deflection could be read to 0·002 mm. The apparatus is shown in Fig. 8. The lower limb of the balance case dipped into a thermostat containing concentrated calcium chloride solution, provided with a thermoregulator coupled to a small heater, and a cooling unit consisting of a glass tube 5 cm. in diameter which could be filled with solid carbon dioxide. By means of a rack and pinion the thermostat tank could be raised or lowered.

It was first shown by means of the microbalance that no change in the character of dehydration occurs at low temperatures. The loss of weight of a small quantity of powdered chrome alum *in vacuo* at −5·6° corresponded to one-half the water content. Changes of weight were observed by following the deflection, and to avoid buoyancy errors initial and final readings were taken in a few mm. of air. It was also shown that a negligible self-cooling occurred: the crystal temperature was, however, slightly higher than that of the thermostat.

Owing to the fact that the whole course of the microbalance beam deflection corresponded to a very small fraction of the weight of the crystal, the method gives the linear velocity at a given percentage decomposition, and both the experimental technique and method of calculation differed from those employed with the helical spring. The correct experimental procedure was found after the following exploratory research, which was subsequently modified. A crystal of known dimensions and weight was nucleated, suspended in a silica cage from the balance, and counterpoised; by means of the side window, silica was then added to the hook on the fibre which held the crystal, the weight of the silica

corresponding to 20% decomposition of the crystal. The apparatus was evacuated at 15° until the microbalance beam began to swing, air was admitted, the cold thermostat was raised into position, and after ½ hour the apparatus was evacuated and readings were taken. More than one run could be made on the same crystal by opening the case and adding quartz to replace the water lost. This procedure gave curved plots of deflection against time with poor reproducibility, a result attributed to the absorption of air by the thick layer of finely divided pseudomorph.

The percentage decomposition studied at first was therefore lowered to 5%, and the apparatus evacuated at 15° with the *thermostat in position* until the beam began to lift off the arrestment. The thermostat was then cooled by adding powdered solid carbon dioxide to the calcium chloride solution, and after 2 hours at the required temperature, during which time the apparatus was evacuated, deflection–time readings were taken. This procedure was necessary to prevent any oscillation of the balance *in vacuo*. Runs could be repeated by opening the balance, adding a small piece of silica to replace the water lost, and repeating the procedure. Percentage decompositions in the region 5—40% were studied. Good straight lines were obtained on plotting deflection against time.

The temperature of the crystal was determined as before: it was also shown that a thermocouple hanging freely inside the evacuated vessel acquired the same temperature as the crystal, and an economy of labour was effected by the use of the hanging thermocouple to measure the crystal temperature, which was slightly higher than that of the bath, possibly owing to radiation.

The linear rate of propagation could be calculated from the area of the interface A, which could be determined from the geometry of the crystal and the percentage decomposition. Since A is virtually constant during a run,

$$-dm/dt = 0{\cdot}2165Au\rho$$

where ρ is the density, and the factor 0·2165 gives the loss of weight of 1 g. of chrome alum on complete decomposition.

Four crystals were studied over a range of temperature. The activation energies for all four were in fair agreement, but there was considerably greater scatter of experimental points than at the higher temperatures; it may be noted that at the "high" temperatures the value of u was obtained as a mean over a large range of decomposition, and hence might be expected to show less scatter than at low temperatures. Values of the temperature-independent factor B were calculated as before. The results for the four crystals are given in Table II, u being in cm. sec.$^{-1}$.

TABLE II.

Crystal *a*: E = 30,400 cals./mole; $B = 6 \times 10^{15}$		Crystal *b*: E = 29,930 cals./mole; $B = 5 \times 10^{15}$		Crystal *c*: E = 29,700 cals./mole; $B = 3 \times 10^{15}$		Crystal *d*: E = 33,100 cals/mole; $B = 1{\cdot}5 \times 10^{19}$	
Crystal temp.	10^6u	Crystal temp.	10^6u	Crystal temp.	10^6u	Crystal temp.	10^6u
− 3·48°	13·3	− 1·71°	32·3	− 2·50°	26·2	−1·70°	24·9
− 3·60	11·4	− 3·30	26·4	− 3·75	16·3	−3·95	21·4
− 5·05	7·76	− 5·50	13·6	− 4·75	29·3	−4·28	23·9
− 6·75	6·04	− 5·80	15·2	− 5·35	16·0	−4·28	12·8
− 8·65	2·94	− 6·30	10·3	− 5·50	15·7	−5·20	14·2
−11·94	1·93	− 7·38	10·0	− 7·85	7·52	−7·05	7·44
		−10·50	5·18	− 8·18	4·39	−7·65	5·19
		−11·45	4·87	− 8·65	6·30	−9·90	3·73
		−12·05	2·54	−12·10	2·91		

Heat of Dissociation.—In normal hydrate dissociations the activation energy for dehydration is equal to the heat of dissociation. For alums, however, it is doubtful if there is a true dissociation pressure, since irreversible phenomena occur on rehydration (Bielanski and Tompkins, *Trans. Faraday Soc.*, 1950, **46**, 1072), and hence the heat of dissociation when measured by the vapour pressure may be anomalous. Following a suggestion by Professor W. E. Garner, we have determined the heat of decomposition by measuring the heats of solution of chrome alum and of the dehydration product, using a thermostated Dewar flask as calorimeter, the calorimeter constant being determined by electrical heating; 0·0028 mole of $K_2SO_4.Cr_2(SO_4)_3.24H_2O$ was dissolved in 14—20 moles of water. The alum was finely powdered and rehydrated over saturated solution in a desiccator and was added to the stirred water in small quantities during 2 minutes. The heat of solution per mole of $K_2SO_4.Cr_2(SO_4)_3.24H_2O$ did not vary with the different dilutions used and was found to be:

$$\Delta H_{298} = 14{\cdot}53,\ 15{\cdot}03,\ 14{\cdot}27,\ 15{\cdot}55,\ 14{\cdot}39;\ \text{mean} = 14{\cdot}75 \text{ kcals.}$$

The heat of solution of the powdered dehydrated product was determined under the same conditions and for the same concentrations of solutions as chrome alum and was found to be:

$$\Delta H_{298} = -12{\cdot}07,\ -11{\cdot}34,\ -12{\cdot}13;\ \text{mean} = -11{\cdot}85 \text{ kcals. per mole of } K_2SO_4.Cr_2(SO_4)_3.12H_2O.$$

It follows that the heat of the reaction:

$$K_2SO_4.Cr_2(SO_4)_3.24H_2O\ (s.) \longrightarrow K_2SO_4.Cr_2(SO_4)_3.12H_2O + 12H_2O\ (l.)$$

is given by ΔH_{298} = 26·60 kcals., or 2·22 kcals. per mole of water lost. Hence the heat of decomposition per mole of water lost for the reaction:

$$K_2SO_4.Cr_2(SO_4)_3.24H_2O\ (s.) \longrightarrow K_2SO_4.Cr_2(SO_4)_3.12H_2O + 12H_2O\ (g.)$$

is given by $\Delta H_{298} = 2{\cdot}22 + 10{\cdot}57 = 12{\cdot}79$ kcals., which is somewhat higher than the figure determined by Cooper and Garner from vapour-pressure measurements at 20—35°, *viz.*, 10·03 kcals. Our value,

however, agrees to within 4% with that calculated from the heats of formation quoted by Bichowsky and Rossini (" The Thermochemistry of the Chemical Substances," Reinhold Publ. Corp., 1936), *viz.*, Q_f $KCr(SO_4)_2.12H_2O$ = 1384·9 kcals.; Q_f $KCr(SO_4)_2.6H_2O$ = 958·0 kcals.; Q_f H_2O (g.) = 57·8 kcals. This gives for the heat of reaction :

$$K_2SO_4.Cr_2(SO_4)_3.24H_2O\ (s.) \longrightarrow K_2SO_4.Cr_2(SO_4)_3.12H_2O + 12H_2O\ (g.)$$

ΔH per mole of water lost = 13·3 kcals. It seems probable, moreover, that the heat of reaction should be greater than the latent heat of vaporization of liquid water.

Discussion.

The activation energy at low temperatures is considerably greater than that at " high " temperatures, and the former value supports that given by Cooper and Garner from their " high " temperature measurements. Two possibilities arise : either our technique gives the true value at high temperatures, so that some change in reaction mechanism occurs on cooling, or, in spite of our improvements in technique the crystal temperature is not known exactly at the " high " temperatures and the low-temperature measurement gives the true activation energy at all temperatures.

It may be thought that a change in mechanism over as small a range of temperature as 15° is unlikely, but Cooper and Garner observed that below 20° unstable nuclei may form, and these have no radial cracks, have a higher activation energy for growth, and occur more frequently below 20° than above. It is noteworthy, in support of the view that the mechanism changes, that the " high " temperature measurements are in better accord with Polanyi and Wigner's expression (*Z. physikal. Chem.*, 1928, Haber Band, 439) than the measurements at low temperatures. This gives for the linear rate of the reaction $u = 2\nu d(E/\boldsymbol{RT})e^{-E/\boldsymbol{RT}}$ where ν is a vibration frequency of a water molecule in the interface and d is a molecular diameter. Now ν is of the order 10^{12} (Bradley, *Phil. Mag.*, 1931, **12**, 290) and hence the temperature-independent factor should be of the order 2×10^6, which is in rough agreement with the value found from the " high " temperature measurements, *viz.*, $3{\cdot}6 \times 10^6$, but much lower than the low temperature value, *viz.*, (3—5) $\times$ 10^{16} (cf. Table II).

Such large values of the temperature-independent factor have received a partial explanation by Garner (*Discuss. Faraday Soc.*, " Crystal Growth " 1949, **5**, 194; cf. also Hartshorne and Roberts, *J.*, 1951, 1097), who assumes that the reaction proceeds relatively rapidly through the crystal mosaic blocks and is then delayed at the gaps between the blocks. If the time taken for the reaction to pass through the block is neglected in comparison with that to bridge the gap, the reaction proceeds a distance w', the width of block and gap, in time $k_4e^{-E/\boldsymbol{RT}}$, *i.e.*, the time taken to bridge the gap, hence $u = (w'/k_4)e^{-E/\boldsymbol{RT}}$. The onus of explanation of the large value of B is then placed on the factor k_4. Although this theory gives a clear explanation of the scatter of experimental results when different crystals were compared, since the block structure may differ, the precise significance of k_4 is not clear. It is possible that the delay at the gap is due to the necessity to nucleate the virgin surface opposite the resultant, but if w' were 10^{-5} cm. and k_4 were 10^{-12} sec.$^{-1}$, w'/k_4 would be 10^7 instead of the observed value at low temperatures (10^{16}); lower values of k_4 would result if nucleation required the simultaneous loss from the surface of more than one water molecule.

A further possibility is that the reaction is governed by the diffusion of water molecules in the solid, so that holes may accumulate round the nuclei (cf. Acock, Garner, Milsted, and Willavoys, *loc. cit.*). This is unlikely in view of the high activation energy measured, since the activation energy for the diffusion would be expected to be less than the heat of dissociation.

On the whole, we are inclined to believe that on cooling there is some change of reaction mechanism, the nature of which requires further experimental study, but in view of the difficulty of measuring crystal temperatures the possibility of spurious temperature measurements in the region of large self-cooling of the crystals cannot be ruled out.

This work was submitted in partial fulfilment of the requirements for a Ph.D. degree at the University of Leeds by one of us (M. M. T. A.), and our thanks are due to the Egyptian Government for a grant to this author. Our thanks are also due to Professor E. G. Cox for his interest and encouragement, and to Professor W. E. Garner for helpful discussions.

This work was begun in October 1946 by M. M. T. Anous and J. Colvin. It was interrupted by a long illness of M. M. T. Anous and was resumed in July 1949. On the death of Dr. J. Colvin in September 1949 the work was resumed by M. M. T. Anous and R. S. Bradley and was completed in June 1951.

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[*Received, July 13th*, 1951.]

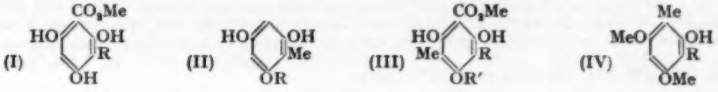
740. *A New Synthesis of* C-*Methylphloroglucinol.*

By Alexander Robertson and W. B. Whalley.

Syntheses of *C*-methylphloroglucinol and some of its derivatives from *s*-trihydroxybenzoates (type I; R = H), by way of the *C*-formyl- (type I; R = CHO) and *C*-methyl-esters (type I; R = Me), are described.

For the preparation of *C*-methylphloroglucinol and its derivatives a variety of methods has been described, *viz.* (*a*) the stepwise or simultaneous substitution of hydroxyl groups for amino-groups in trinitrotoluene (*e.g.* Weidel and Wenzel, *Monatsh.*, 1898, **19**, 223) or aminonitrotoluenes (Curd and Robertson, *J.*, 1933, 437), (*b*) the decarboxylation of suitable *C*-alkylated *s*-trihydroxybenzoic acids obtained by the *C*-alkylation of *s*-trihydroxybenzoic acid (Herzig *et al.*, *Monatsh.*, 1888, **9**, 217, 882; 1889, **10**, 735; 1893, **14**, 376; 1900, **21**, 852, 866; 1901, **22**, 215; 1902, **23**, 81; Margulies, *ibid.*, 1888, **9**, 1045; 1889, **10**, 459; Pollak, *ibid.*, 1897, **18**, 745; Will, *Ber.*, 1884, **17**, 2107; Curd and Robertson, *loc. cit.*), (*c*) the direct synthesis from the requisite aliphatic components (cf. Curd and Robertson, *loc. cit.*), and (*d*) the simultaneous catalytic reduction and debenzylation of suitable benzylated phloroglucinaldehydes (*e.g.* Birch, Flynn, and Robertson, *J.*, 1936, 1834) with a palladium–charcoal catalyst or the reduction of phloroglucinaldehyde and its *O*-monomethyl ether with a Raney nickel catalyst (McGookin, Robertson, and Simpson, *J.*, 1951, 2021). With the possible exception of the last method these procedures are more or less unsatisfactory for the preparation of this phenol and its derivatives in quantity. The present investigation was therefore initiated with the objective of providing a new route to *C*-methylphloroglucinol and its derivatives, required for several synthetical investigations in progress in these laboratories.

The method now described utilises the easy reduction of the appropriate formyltrihydroxybenzoate by the Clemmensen method, followed by the hydrolytic elimination of the carbomethoxy-residue, giving high yields of the requisite phenols.



Thus, *e.g.*, the reduction of methyl 3-formyl-2 : 4 : 6-trihydroxybenzoate (I; R = CHO) readily gives methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (I; R = Me) which on hydrolytic decomposition with aqueous alkali furnishes *C*-methylphloroglucinol (II; R = H). Similarly, methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (I; R = Me) furnishes 2 : 4 : 6-trihydroxy-*m*-xylene by way of the intermediates (III; R = CHO, R′ = H) and (III; R = Me, R′ = H), respectively, and methyl 3-formyl-2 : 6-dihydroxy-4-methoxy-5-methylbenzoate (III; R = CHO, R′ = Me) (Robertson and Whalley, *J.*, 1950, 1882) yields 4 : 6-dihydroxy-2-methoxy-*m*-xylene by way of (III; R = R′ = Me).

A new route to 2-hydroxy-4 : 6-dimethoxytoluene (IV; R = H) is described; the reduction of *C*-formylphloroacetophenone provides a convenient route to *C*-methylphloroacetophenone (cf. Robertson, Whalley, and Yates, *J.*, 1950, 3117).

Experimental.

Methyl 3-Formyl-2 : 4 : 6-trihydroxybenzoate.—A solution of methyl 2 : 4 : 6-trihydroxybenzoate (Herzig, Wenzel, and Graetz, *Monatsh.*, 1902, **23**, 86) (5 g.) and hydrogen cyanide (10 ml.) in ether (200 ml.) was saturated with hydrogen chloride at 0°, and 24 hours later the crystalline aldimine salt was collected, washed with ether, and rapidly heated with water (300 ml.) to 100°. *Methyl 3-formyl-2 : 4 : 6-trihydroxybenzoate* separated from the cooled hydrolysate, and on crystallisation from methanol formed needles (5 g.), m. p. 169°, which were sparingly soluble in alcohol, almost insoluble in benzene or light petroleum, and having a red-brown ferric reaction in alcohol (Found : C, 51·1; H, 3·9. $C_9H_8O_6$ requires C, 50·9; H, 3·7%). The *oxime* formed needles, m. p. 201° (decomp.), from dilute methanol (Found : N, 6·2. $C_9H_9O_6N$ requires N, 6·2%).

C-Methylphloroglucinol.—A solution of the foregoing formyl-ester (10 g.) in warm methanol (250 ml.) was added dropwise during 20 minutes to warm concentrated hydrochloric acid (125 ml.), containing water (35 ml.) and amalgamated zinc dust (100 g.), and the mixture then heated under reflux for 15 minutes, cooled, and extracted with ether, giving methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate which

separated from benzene–light petroleum (b. p. 60—80°) in rosettes of prisms (8·7 g.), m. p. 146° (cf. Herzig, Wenzel, and Graetz, *Monatsh.*, 1902, **23**, 105). On being boiled with 10% aqueous potassium hydroxide (100 ml.) in nitrogen for 3 hours this ester gave *C*-methylphloroglucinol (6·6 g.), m. p. 214°, which was isolated with ether.

Similarly, the hydrolytic decomposition of methyl 2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (Robertson and Whalley, *loc. cit.*) gave an almost quantitative yield of hydrated *C*-methylphloroglucinol *β*-monomethyl ether, m. p. 88—89°, which on sublimation at 140°/0·1 mm. gave the anhydrous phenol, m. p. 119° (Found : C, 62·5; H, 6·7. Calc. for $C_8H_{10}O_3$: C, 62·3; H, 6·5%) (cf. Boehm, *Annalen*, 1898, **302**, 187, who gives m. p. 117—118°).

2-Hydroxy-4 : 6-dimethoxytoluene (IV; R = H).—Methyl sulphate (8 g.) was added gradually during 3 hours to a boiling solution of methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (7 g.) in acetone (100 ml.) containing potassium carbonate (10 g.), and the mixture then heated for 1 hour. On isolation methyl 2-hydroxy-4 : 6-dimethoxy-3-methylbenzoate (IV; R = CO_2Me) (6 g.) separated from methanol in prisms, m. p. 146° (Robertson and Curd, *loc. cit.*, give m. p. 144—145°). Hydrolysis of this ester (3 g.) with boiling 20% potassium hydroxide solution (20 ml.) during 2 hours gave 2-hydroxy-4 : 6-dimethoxytoluene (2·2 g.), m. p. 66° (Robertson and Curd, *loc. cit.*, record m. p. 67—68°).

Methyl 3-Formyl-2 : 4 : 6-trihydroxy-5-methylbenzoate.—The interaction of methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (4 g.) and hydrogen cyanide (9 ml.) in ether (200 ml.), saturated at 0° with hydrogen chloride, followed by hydrolysis of the aldimine salt with water at 100° furnished *methyl 3-formyl-2 : 4 : 6-trihydroxy-5-methylbenzoate* which separated from methanol in slender prisms (4·3 g.), m. p. 168°, having a plum-coloured ferric reaction in alcohol (Found : C, 52·9; H, 4·4. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4%). The *oxime* formed small needles, m. p. 195°, from dilute methanol (Found : N, 6·2. $C_{10}H_{11}O_6N$ requires N, 5·8%).

CC-Dimethylphloroglucinol.—Reduction of methyl 3-formyl-2 : 4 : 6-trihydroxy-5-methylbenzoate (3 g.) by the method employed for methyl 3-formyl-2 : 4 : 6-trihydroxybenzoate gave methyl 2 : 4 : 6-trihydroxy-3 : 5-dimethylbenzoate which crystallised from dilute methanol in long prisms (2·7 g.), m. p. 139° (Found : C, 56·5; H, 5·4. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7%) (cf. Herzig, Wenzel, and Altmann, *Monatsh.*, 1901, **22**, 219), and which, with boiling 10% aqueous potassium hydroxide, gave an almost quantitative yield of *CC*-dimethylphloroglucinol, m. p. 162° after purification from benzene–ethyl acetate (Weidel and Wenzel, *Monatsh.*, 1898, **19**, 237, record m. p. 161°).

4 : 6-Dihydroxy-2-methoxy-m-xylene.—Reduction of methyl 3-formyl-2 : 6-dihydroxy-4-methoxy-5-methylbenzoate (Robertson and Whalley, *loc. cit.*) (0·5 g.), dissolved in methanol (15 ml.), with amalgamated zinc (5 g.) and a boiling mixture of concentrated hydrochloric acid (15 ml.) and water (5 ml.) for 15 minutes gave methyl 2 : 6-dihydroxy-4-methoxy-3 : 5-dimethylbenzoate which formed prisms (0·4 g.), m. p. 99°, from dilute methanol, and had a green ferric reaction (Found : C, 58·0; H, 6·1. Calc. for $C_{11}H_{14}O_5$: C, 58·4; H, 6·2%) (cf. Herzig *et al.*, *Monatsh.*, 1902, **23**, 102, who give m. p. 96—98°). On elimination of the carbomethoxy-group, this ester (0·3 g.) gave 4 : 6-dihydroxy-2-methoxy-*m*-xylene (0·2 g.), m. p. 145° (Found : C, 64·0; H, 7·0. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·1%) (cf. Boehm, *Annalen*, 1903, **329**, 294, who gives m. p. 147—148°).

3-Formyl-2 : 4 : 6-trihydroxy-5-methylacetophenone.—This compound was prepared by the interaction of *C*-methylphloroacetophenone (2 g.), zinc cyanide (2 g.), and hydrogen cyanide (5 ml.) in ether, saturated at 0°, for 24 hours followed by rapid heating to boiling of the aldimine salt with water (150 ml.). The *formyl-ketone* separated from dilute methanol in rosettes of almost colourless needles (2 g.), m. p. 134°, having a red-brown ferric reaction in alcohol (Found : C, 57·4; H, 5·1. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 294—295° (decomp.), from much acetic acid (Found : N, 14·1. $C_{16}H_{14}O_8N_4$ requires N, 14·4%).

C-Formylphloroacetophenone, m. p. 182—183°, was prepared in excellent yield by the same method, without the aid of aluminium chloride as described by Shah and Shah (*J.*, 1939, 949), who give m. p. 180—182°. On being gently heated with a mixture of methanol (40 ml.), hydrochloric acid (25 ml.), water (15 ml.), and amalgamated zinc (20 g.) until a test portion gave a negative reaction with 2 : 4-dinitrophenylhydrazine sulphate solution (3—4 minutes), this formyl-ketone (4·5 g.) gave *C*-methylphloroacetophenone (2·2 g.) in almost colourless needles, m. p. 210—211°, identical with an authentic specimen (Curd and Robertson, *loc. cit.*).

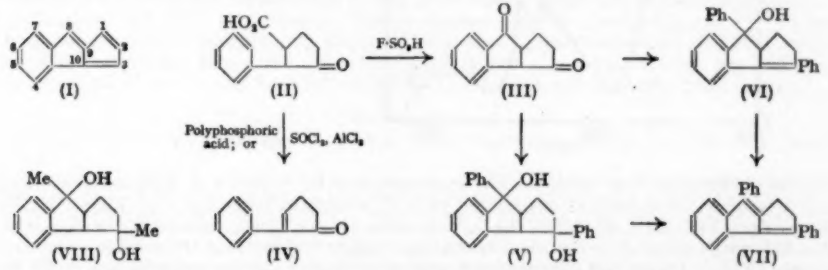
UNIVERSITY OF LIVERPOOL. [*Received, August 8th*, 1951.]

741. *Attempts to Prepare New Aromatic Systems. Part IV.** cyclo*Pent*[a]*indene.*

By Wilson Baker, F. Glockling, and J. F. W. McOmie.

*cyclo*Dehydration of 3-keto-2-phenyl*cyclo*pentane-1-carboxylic acid (II) to 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-diketo*cyclo*pent[*a*]indene (III) is readily brought about by fluorosulphonic acid, and this diketone is a promising intermediate for the synthesis of *cyclo*pent[*a*]indene (I). The diketone reacts with phenylmagnesium iodide and with methylmagnesium iodide, giving hexahydro-3 : 8-dihydroxy-3 : 8-diphenyl- and -3 : 8-dimethyl-*cyclo*pent[*a*]indenes (V and VIII); the former is readily dehydrated to the bright orange hydrocarbon, 1 : 2-dihydro-3 : 8-diphenyl*cyclo*pent[a]indene (VII). Catalytic reduction of the diketone has yielded the diol (IX), and the two isomeric hydroxy-ketones (X) and (XI). Nitrosation of the diketone gave 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-diketo-2-oximino*cyclo*pent[*a*]indene (XIII), from which the trioximino-compound was obtained by reaction with hydroxylamine.

Preliminary experiments directed towards the synthesis of *cyclo*pent[*a*]indene (I) were described in Parts I (Baker and Leeds, *J.*, 1948, 974) and III (Baker and Jones, *J.*, 1951, 787) of this series. A satisfactory synthesis of a ketone with the required carbon skeleton, namely 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-keto*cyclo*pent[*a*]indene, was recorded in Part III, and this was reduced to 1 : 2 : 3 : 8 : 9 : 10-hexahydro*cyclo*pent[*a*]indene. Direct dehydrogenation of this hydrocarbon to *cyclo*pent[*a*]indene (I) could not be accomplished in spite of many attempts, showing that either the aromatic ring system of *cyclo*pent[*a*]indene is not formed so readily as those of polycyclic, purely benzenoid compounds, or that if formed it is not stable under the conditions employed. It was, therefore, decided to investigate methods of approach which would involve only mild reactions such as dehydration, exhaustive methylation, or loss of hydrogen halide in the final steps. Preliminary experiments directed towards the same end have also been described by others (Clemo, Groves, Munday, and Swan, *J.*, 1951, 863; Groves and Swan, *J.*, 1951, 867; Dahn, *Helv. Chim. Acta*, 1951, **34**, 1087).



In the following account stereochemical problems are ignored though it is probable that the two five-membered rings are fused in the *cis* position in all the hexahydro*cyclo*pent[*a*]indene derivatives described.

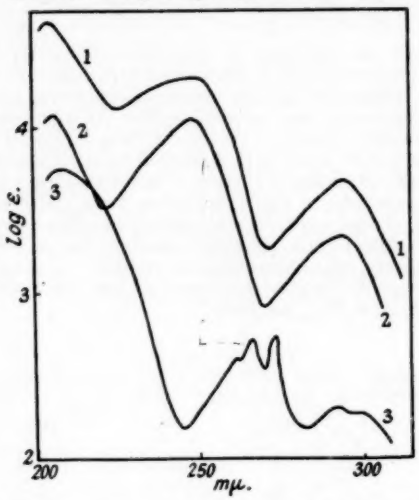
The most promising intermediate appeared to be 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-diketo*cyclo*pent[*a*]indene (III), which we had previously attempted to make by *cyclo*dehydration of 3-keto-2-phenyl*cyclo*pentane-1-carboxylic acid (II) (Part III, p. 789) by using a mixture of phosphoric anhydride and syrupy phosphoric acid. These reactions led, however, to loss of the elements of formic acid with production of 2-phenyl*cyclo*pent-2-en-one (IV), and the same result has now been obtained by treating the acid (II) with polyphosphoric acid (see Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962, 2965), and with thionyl chloride followed by aluminium chloride. The final successful production of the diketone (III) from the acid (II) by dehydration with fluorosulphonic acid was briefly reported in a recent note (Baker, Coates, and Glockling, *J.*, 1951, 1376) and, as with other cyclodehydrations with fluorosulphonic acid,

* Part III, *J.*, 1951, 787.

the reaction temperature is critical. Almost complete sulphonation occurs at 100°, and practically no reaction at room temperature; the reaction is best carried out initially at 50—60°, at which temperature little sulphonation occurs and about 50% of the acid is recovered unchanged. The yield of the diketone (III) is 40%, or 82% allowing for the recovered acid.

Reaction of the diketone (III) with two equivalents of phenylmagnesium bromide gave 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-dihydroxy-3 : 8-diphenyl*cyclo*pent[*a*]indene (V), though in one experiment which has not so far been repeated a pale yellow, mono-anhydro-derivative of (V) was isolated. The colour of this compound, and the fact that the hydrogen atom in position 10 of the diol (V) is likely to be more reactive than that in position 9 or than the two hydrogen atoms in position 2, makes it likely that this anhydro-derivative is the most fully conjugated possible, namely the stilbene derivative 1 : 2 : 8 : 9-tetrahydro-8-hydroxy-3 : 8-diphenyl*cyclo*pent[*a*]indene (VI). Dehydration of the diol (V) takes place very readily by boiling it in xylene solution with anhydrous copper sulphate, and yields a bright orange hydrocarbon which must be highly conjugated and is regarded as 1 : 2-dihydro-3 : 8-diphenyl*cyclo*pent[*a*]indene (VII). This orange hydrocarbon is also obtained from the unsaturated olefin

Ultra-violet absorption spectra in ethanolic solution.



Curve 1. 1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3 : 8-*diketo*cyclo*pent*[a]*indene* (III).

Curve 2. 1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3-*hydroxy*-8-*keto*cyclo*pent*[a]*indene* (X).

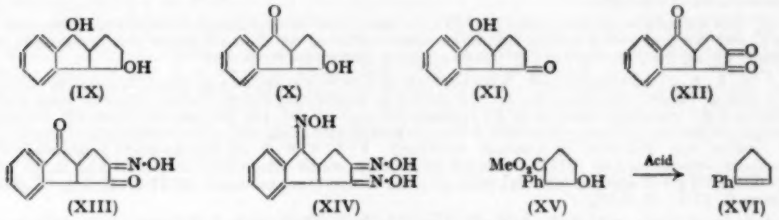
Curve 3. 1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-8-*hydroxy*-3-*keto*cyclo*pent*[a]*indene* (XI).

(VI) by sublimation in a vacuum. The hydrocarbon (VII) is both a 1 : 4-diphenylbutadiene and a stilbene; it is most closely related to 1 : 1 : 4-triphenylbutadiene, $CPh_2{:}CH{\cdot}CH{:}CHPh$ (Staudinger, *Ber.*, 1909, **42**, 4285), the lack of colour of which lends support to the suggestion that the orange-coloured hydrocarbon has the most highly conjugated of the possible structures, namely (VII). The central five-membered ring of (VII) is of fulvene character and would be expected to shift the absorption bands into the visible part of the spectrum. Catalytic hydrogenation of (VII) could not be achieved by using either palladium black or Adams's platinum oxide catalyst at room temperature.

Methylmagnesium iodide reacted with the diketone (III) to give 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-dihydroxy-3 : 8-dimethyl*cyclo*pent[*a*]indene (VIII), and this compound readily yielded a liquid mono-anhydro-derivative which may not be entirely homogeneous; the structure is unknown, as five isomerides can result from simple loss of water. Attempts to obtain a hydrocarbon from (VIII) by complete dehydration led to high molecular weight material.

Catalytic reduction of the diketone (III) with two mols. of hydrogen gave the diol, 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-dihydroxy*cyclo*pent[*a*]indene (IX), but with one mol. of hydrogen the hydroxy-ketone, 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3-hydroxy-8-keto*cyclo*pent[*a*]-indene (X), was isolated. The structure assigned to (X) is based on the similarity of its ultra-violet absorption curve to that of indane-1-one (Ramart Lucas, *Bull. Soc. chim.*, 1935, [5], **2**,

327; Biquard, *ibid.*, 1941, [5], **8**, 55). In one experiment the catalytic reduction of (III) took place slowly and incompletely, and led to the isolation of the isomeric hydroxy-ketone 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-hydroxy-3-keto*cyclo*pent[*a*]indene (XI), the absorption spectrum of which was quite unlike that of the conjugated ketone (X), and closely resembled that of indane-2-one (Biquard, *loc. cit.*). Ultra-violet absorption curves for the diketone (III) and the hydroxy-ketones (X) and (XI) are shown in the figure. Reduction of the diketone (III) by the Ponndorf method gave a mono-anhydro-derivative of the diol (IX), which is probably 1 : 2 : 8 : 9-tetrahydro-8-hydroxy*cyclo*pent[*a*]indene, but further dehydration led to high molecular weight material.



In a direct attempt to introduce a third oxygen atom into the diketone (III) it was oxidised with selenium dioxide but no definite products could be isolated. Nitrosation with amyl nitrite, however, gave 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-diketo-2-oximino*cyclo*pent[*a*]indene (XIII), but attempts to hydrolyse this to the triketone (XII) by means of hydrochloric acid in presence of formalin were not successful. With the object of obtaining a derivative of triaminohexahydro*cyclo*pent[*a*]indene which might be converted into *cyclo*pent[*a*]indene by exhaustive methylation, the oximino-compound (XIII) was converted into its dioxime, 1 : 2 : 3 : 8 : 9 : 10-hexahydro-2 : 3 : 8-trioximino*cyclo*pent[*a*]indene (XIV); the subsequent steps have not yet been fully investigated.

Before the cyclisation of the acid (II) to the diketone (III) had been achieved by means of fluorosulphonic acid, it was hoped to prevent the loss of the elements of formic acid during attempted cyclodehydration by first reducing the carbonyl group in (II) to a secondary alcohol. Catalytic reduction of the methyl ester of (II) gave methyl 3-hydroxy-2-phenyl*cyclo*pentane-1-carboxylate (XV), but this substance showed marked instability towards acids, being converted even on boiling with dilute hydrochloric acid into 1-phenyl*cyclo*pent-1-ene (XVI) with loss of carbon dioxide and water. The same product was also obtained when the acid (II) was submitted to the normal Ponndorf conditions of reduction and isolation of the product.

Experimental.

M.p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3 : 8-*diketo*cyclo*pent*[a]*indene* (III).—3-Keto-2-phenyl*cyclo*pentane-1-carboxylic acid (II) (11·8 g.) was treated with fluorosulphonic acid (35 c.c.) in two portions so that the temperature rose spontaneously to 50—60°. The homogeneous mixture was left at room temperature for 1¾ hours with occasional shaking, poured into water (500 c.c.), and after 1 hour extracted thoroughly with ether. The extract was shaken with excess of aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and distilled, leaving 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-3 : 8-*diketo*cyclo*pent*[a]*indene* (III) (4·33 g.), m. p. 86—88°. For analysis a portion was distilled at 1 mm. pressure (bath-temp. 160°) and then crystallised from light petroleum (b. p. 80—100°), giving long needles, m. p. 91° (Found: C, 77·5; H, 5·3. $C_{13}H_{14}O_2$ requires C, 77·4; H, 5·4%). The aqueous alkaline solution yielded unchanged keto-acid (II) (6·03 g.), m. p. and mixed m. p. 115—116°.

The *dioxime* of the diketone (III) was twice crystallised from light petroleum (b. p. 60—80°) containing a little ethanol, and formed needles, m. p. 167° (Found, in material dried at 78° *in vacuo*: C, 66·7; H, 5·8; N, 13·0. $C_{13}H_{16}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3 : 8-*dihydroxy*-3 : 8-*diphenyl*cyclo*pent*[a]*indene* (V).—The diketone (III) (4·0 g.) in dry benzene (50 c.c.) was added slowly to a solution of phenylmagnesium bromide prepared from bromobenzene (8·1 g.) and magnesium (1·25 g.) in dry ether (25 c.c.), the mixture boiled for 10 minutes, left overnight, and, after the addition of aqueous ammonium chloride, extracted several times with ether. The extracts yielded a yellow oil (7·1 g.), which when dissolved in ethanol yielded colourless needles (4·3 g.), m. p. 169—170°, of 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-3 : 8-*dihydroxy*-3 : 8-*diphenyl*-cyclo*pent*[a]*indene* (V) (Found, in material crystallised three times from ethanol: C, 83·9; H, 6·4. $C_{24}H_{22}O_2$ requires C, 84·2; H, 6·4%).

1 : 2 : 8 : 9-*Tetrahydro*-8-*hydroxy*-3 : 8-*diphenyl*cyclo*pent*[a]*indene* (VI).—The diketone (III) (1·0 g.) in benzene (15 c.c.) was added to a solution of phenylmagnesium bromide, prepared from bromobenzene

(1·7 g.) and magnesium (0·26 g.) in ether (30 c.c.), the mixture boiled for 5 minutes, and the product isolated as in the previous case. The yellow solid (1·2 g.), after several crystallisations first from aqueous ethanol (charcoal) and then from ethanol, formed pale yellow needles, m. p. 161—162°, of 1 : 2 : 8 : 9-*tetrahydro*-8-*hydroxy*-3 : 8-*diphenylcyclopent*[a]*indene* (VI) (Found: C, 88·3; H, 6·2. $C_{24}H_{20}O$ requires C, 88·9; H, 6·2%).

1 : 2-*Dihydro*-3 : 8-*diphenylcyclopent*[a]*indene* (VII).—(*a*) The dihydroxy-compound (V) (0·27 g.) was boiled for 4 hours in dry xylene (15 c.c.) in the presence of anhydrous copper sulphate (1·0 g.) and then filtered, and the residue washed with ether. Evaporation of the solvents and crystallisation of the residue from ethanol gave 1 : 2-*dihydro*-3 : 8-*diphenylcyclopent*[a]*indene* (VII) as bright orange needles (0·21 g.), m. p. 168—174°. Further purification first by sublimation *in vacuo* and then by two crystallisations from ethanol gave the pure compound, m. p. 180° (Found: C, 94·1; H, 5·8. $C_{24}H_{18}$ requires C, 94·1; H, 5·9%).

(*b*) The monohydroxy-compound (VI) (0·1 g.) was heated in a sublimation apparatus (160—180°/0·1 mm.), and the orange-red, glassy sublimate which collected on the cold finger was crystallised from ethanol, giving the hydrocarbon (VII) (0·04 g.), m. p. and mixed m. p. 180°.

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3 : 8-*dihydroxy*-3 : 8-*dimethylcyclopent*[a]*indene* (VIII).—The diketone (III) (2·0 g.) in dry benzene (15 c.c.) was added to methylmagnesium iodide prepared from methyl iodide (3·7 g.) and magnesium (0·62 g.) in ether (10 c.c.). After the mixture had been left overnight, aqueous ammonium chloride was added, the oil extracted with ether, and after the removal of the solvent, the residue was dissolved in aqueous methanol. 1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3 : 8-*dihydroxy*-3 : 8-*dimethylcyclopent*[a]*indene* (VIII) separated as needles, which after recrystallisation had m. p. 110—111° (yield 1·4 g.) (Found, in material dried at room temperature *in vacuo*: C, 77·3; H, 7·9. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%).

Anhydro-derivative of 1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3 : 8-*dihydroxy*-3 : 8-*dimethylcyclopent*[a]*indene*.—(*a*) The dihydroxy-compound (VIII) (0·34 g.) was heated at 120° in a cold-finger sublimation apparatus at 1 mm. pressure. Rapid evolution of steam occurred, and the residue then distilled (bath temp. 140—160°) as a thick, pale yellow oil (0·22 g.). This *anhydro*-derivative was similarly redistilled with partial conversion into a residual orange glass (Found, in distillate: C, 84·0; H, 8·5. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%).

(*b*) The dihydroxy-compound (VIII) (1·6 g.) was boiled in toluene (20 c.c.) with anhydrous copper sulphate (3 g.) for 8 hours. The toluene solution yielded what is probably the same anhydro-derivative as a yellow oil (0·2 g.), b. p. 110°/1 mm. (Found: C, 84·8; H, 8·4%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3 : 8-*dihydroxycyclopent*[a]*indene* (IX).—The diketone (III) (0·5 g.) in ethanol (50 c.c.) was shaken at atmospheric pressure with hydrogen in the presence of Raney nickel (1 g.) for 4 hours, when 2 mols. of hydrogen had been absorbed. The filtered solution yielded an oil which was distilled at 0·5 mm. pressure (bath temp. 200°). The colourless distillate solidified, and was crystallised from benzene–light petroleum (b. p. 60—80°), giving 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-3 : 8-*dihydroxycyclopent*[a]*indene* (IX) as needles, m. p. 75° (Found: C, 75·8; H, 7·4. $C_{13}H_{14}O_2$ requires C, 75·8; H, 7·4%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3-*hydroxy*-8-*keto*cyclo*pent*[a]*indene* (X).—The diketone (III) (1·05 g.) in ethanol (20 c.c.) was hydrogenated as in the previous experiment, but the reaction was stopped after the uptake of 1 mol. of hydrogen. The resulting 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-3-*hydroxy*-8-*keto*cyclo*pent*[a]*indene* (X) (0·6 g.) separated from benzene–light petroleum (b. p. 60—80°) in rectangular prisms, m. p. 115—116° (Found: C, 76·3; H, 6·5. $C_{13}H_{16}O_2$ requires C, 76·6; H, 6·4%). It may be sublimed unchanged under diminished pressure. The 2 : 4-*dinitrophenylhydrazone*, prepared by Brady's method, separated from benzene as red needles, m. p. 208—209° (Found, in twice crystallised material: C, 59·2; H, 4·5; N, 15·4. $C_{19}H_{18}O_5N_4$ requires C, 58·8; H, 4·4; N, 15·2%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-8-*hydroxy*-3-*keto*cyclo*pent*[a]*indene* (XI).—A somewhat crude specimen of the diketone (III) (5·0 g.) in ethanol (100 c.c.) was hydrogenated at atmospheric pressure in presence of Raney nickel (0·5 g.). After 15 hours, absorption of only 2/3 mol. of hydrogen had taken place, and concentration of the solution (to 25 c.c.) and further slow evaporation at room temperature led to the separation of crystalline material (0·75 g.). After being twice crystallised from benzene–light petroleum (b. p. 60—80°) the 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-8-*hydroxy*-3-*keto*cyclo*pent*[a]*indene* (XI) separated as needles, m. p. 135° (Found: C, 76·5; H, 6·4. $C_{13}H_{16}O_2$ requires C, 76·6; H, 6·4%). The 2 : 4-*dinitrophenylhydrazone* was twice crystallised from ethanol giving yellow needles, m. p. 208° (Found: C, 59·4; H, 4·1; N, 15·4. $C_{19}H_{18}O_5N_4$ requires C, 58·8; H, 4·4; N, 15·2%).

1 : 2 : 8 : 9-*Tetrahydro*-8-*hydroxy*cyclo*pent*[a]*indene* (?).—The diketone (III) (6·1 g.), freshly distilled aluminium *iso*propoxide (13·5 g.), and dry *iso*propyl alcohol (100 c.c.) were boiled for 6½ hours, while 70 c.c. of distillate were collected. The residue was poured on ice and dilute hydrochloric acid and extracted with ether, and the extracts yielded a product which distilled as a viscous yellow oil (2·84 g.), b. p. 148—151°/1 mm. Redistillation resulted in the formation of much high molecular weight material (Found, in distillate: C, 83·6; H, 7·6. $C_{13}H_{12}O$ requires C, 83·7; H, 7·0%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-3 : 8-*diketo*-2-*oximino*cyclo*pent*[a]*indene* (XIII).—The diketone (III) (10·5 g.), freshly distilled amyl nitrite (9·0 g.), and ethanol (100 c.c.) were treated dropwise at −10° with concentrated hydrochloric acid (2·4 c.c.). The mixture was allowed to reach room temperature, warmed to 50° for 10 minutes, and poured into water (250 c.c.)–ether (100 c.c.). The pink solid which collected at the interface of the two liquids was collected (3·02 g.) and crystallised first from benzene containing a little ethanol and then from benzene, giving 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-3 : 8-*diketo*-2-*oximino*cyclo*pent*[a]*indene* (XIII) as pale yellow needles, m. p. 202—204° (decomp.) (Found: C, 67·2; H, 4·5; N, 6·6. $C_{13}H_9O_3N$ requires C, 67·0; H, 4·2; N, 6·5%). A further quantity (1·26 g.) of (XIII) was obtained by keeping the aqueous-ethereal mixture at 0° for 48 hours.

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-2 : 3 : 8-*trioximino*cyclo*pent*[a]*indene* (XIV).—The crude monooximino-compound (XIII) (0·9 g.), hydroxylamine hydrochloride (1·5 g.), sodium acetate (1·5 g.), water (25 c.c.), and ethanol (25 c.c.) were boiled for 4 hours. After cooling and dilution with water the 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-2 : 3 : 8-*trioximino*cyclo*pent*[a]*indene* (XIV) (1·0 g.) was collected and crystallised three times from aqueous ethanol, being obtained as needles, m. p. 265° (decomp.) (Found: C, 59·1; H, 4·9; N, 17·4. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5; N, 17·2%).

Methyl 3-*Hydroxy*-2-*phenyl*cyclo*pentane*-1-*carboxylate* (XV).—Methyl 3-keto-2-phenyl*cyclo*pentane-1-carboxylate (Baker and Jones, *J.*, 1951, 792) (5·0 g.) in methanol (150 c.c.) was shaken with hydrogen at 6 atmospheres' pressure in the presence of Raney nickel (1 g.) for 7 hours. The *methyl* 3-*hydroxy*-2-*phenyl*cyclo*pentane*-1-*carboxylate* was isolated as a colourless, viscous oil, b. p. 136°/1 mm. (4·8 g.) (Found: C, 71·2; H, 7·2. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

1-*Phenyl*cyclo*pent*-1-*ene* (XVI).—The preceding ester (XV) (4·6 g.), concentrated hydrochloric acid (100 c.c.), and water (100 c.c.) were boiled for 7 hours, and then steam-distilled. The steam-distillate was extracted with ether, and the extracts washed with aqueous sodium hydrogen carbonate, dried, and distilled, yielding 1-phenyl*cyclo*pent-1-ene as a colourless oil (1·35 g.), b. p. 78—80°/2 mm., which soon solidified and then had m. p. 25° (von Braun, *Ber.*, 1927, **60**, 2555, records m. p. 23°). The sodium hydrogen carbonate extract gave only a trace of acidic material. The 1-phenyl*cyclo*pent-1-ene was characterised by catalytic reduction whereupon 1 mol. of hydrogen was taken up, giving phenyl*cyclo*pentane, b. p. 215—216°/760 mm. (lit. b. p. 213—215°/760 mm.), and by oxidation with alkaline potassium permanganate to γ-benzoylbutyric acid, m. p. 127—128° (Wislicenus and Kuhn, *Annalen*, 1898, **302**, 218, record m. p. 127·5°).

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742. *Electrometric Titration of the Sodium Salts of Deoxyribonucleic Acids. Part I.*

By W. A. LEE and A. R. PEACOCKE.

The sodium salts of the deoxypentose nucleic acids of calf thymus, herring sperm, wheat germ, and mouse sarcoma have been titrated electrometrically at 25° and the effects of dialysis and of drying have been examined. The forward-titration curves of the original nucleic acid solutions (pH 6—7) differ markedly from the back-titration curves after acid and alkali treatment. The back-titration curves from pH 2 and from pH 12 differ significantly from each other and this can be explained in terms of hydrogen bonding or, more probably, by the existence of a slow hydrolysis of some internucleotide linkages at alkaline pH.

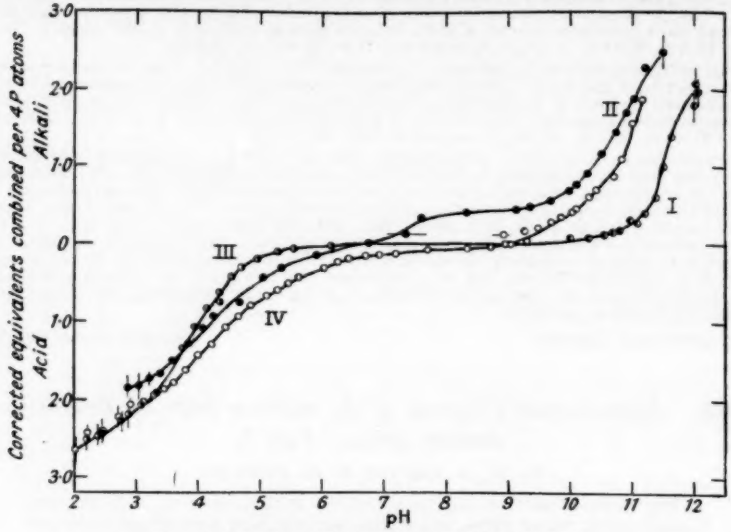
By combining analyses and titration data, an estimate of the proportions of the various types of phosphoryl linkages has been made and this implies a higher frequency of branching of the polynucleotide chain, at triply bonded phosphorus atoms, than has previously been assumed. The effect of acid and alkali on various labile linkages and the dissociation of these substances as polyelectrolytes are discussed.

IN recent years techniques have been developed which have made it possible to isolate deoxyribonucleic acids from biological sources with the minimum of degradation. These methods are mainly variations of the procedure of Mirsky and Pollister (*Proc. Nat. Acad. Sci.*, 1942, **28**, 344) whereby deoxyribonucleoprotein can be isolated under neutral conditions from a variety of tissues by utilising the dependence of its solubility in water on the concentration of sodium chloride. The protein may then be separated from the nucleic acid by removing it as a gel with chloroform (Sevag, Lackmann, and Smolens, *J. Biol. Chem.*, 1938, **124**, 425) or by precipitating it with saturated sodium chloride (Hammarsten, *Biochem. Z.*, 1924, **144**, 383). Both methods finally yield white fibrous deoxyribonucleic acid, which dissolves to give highly viscous, non-Newtonian solutions exhibiting negative streaming birefringence (Gulland, Jordan, and Threlfall, *J.*, 1947, 1129; Jordan, 27th Ann. Rep. British Empire Cancer Campaign, 1949, 26; Signer and Schwander, *Helv. Chim. Acta*, 1949, **32**, 853).

It has been observed (Gulland, Jordan, and Taylor, *J.*, 1947, 1131; Cosgrove and Jordan, *J.*, 1949, 1413; Signer and Schwander, *loc. cit.*) that the curves obtained when neutral solutions of the sodium salts of deoxyribonucleic acids, isolated by such mild methods, are first titrated to pH 2·5 and pH 12 differ markedly from those obtained on back-titration with alkali and acid, respectively. Gulland, Jordan, and Taylor (*loc. cit.*) attributed this difference to the existence of hydrogen bonds between titratable groups and, on this hypothesis, titration curves afford a useful method for examining the state of hydrogen bonding of deoxyribonucleic acids.

FIG. 1.

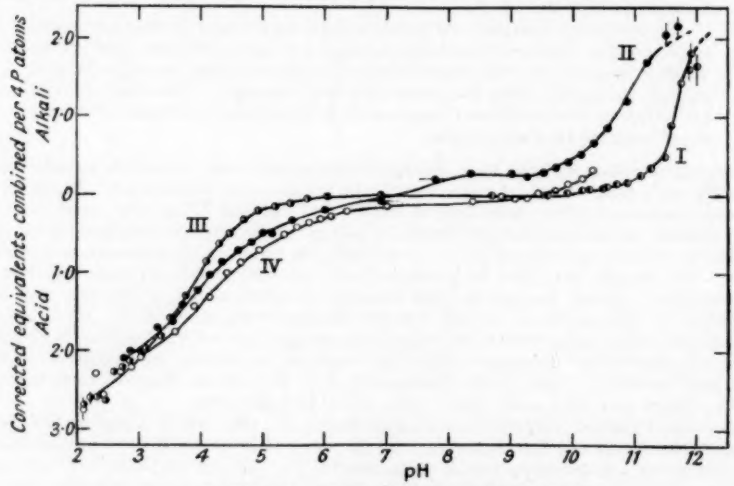
The titration curve of the sodium salt of deoxyribonucleic acid from calf thymus (T_3)—undried.



◐ I. *Titration with alkali from* pH 7·2 *to* pH 12·1.
● II. *Back-titration with acid from* pH 12·1.
◑ III. *Titration with acid from* pH 6·8 *to* pH 2·0.
⊙ IV. *Back-titration with alkali from* pH 2·0.

FIG. 2.

The titration curve of the sodium salt of deoxyribonucleic acid from herring sperm (H_1)—undried



◐ I. *Titration with alkali from* pH 6·9 *to* pH 12·0.
● II. *Back-titration with acid from* pH 12·0.
◑ III. *Titration with acid from* pH 6·9 *to* pH 2·0.
⊙ IV. *Back-titration with alkali from* pH 2·0.

The present work on titration curves forms part of an investigation of deoxyribonucleic acids isolated from various sources by mild neutral methods. The effects on their structures of procedures used in isolating nucleic acids have also been examined. Dialysis has little effect, drying a more noticeable one, while ultrasonic irradiation causes a breakdown of the hydrogen bonding, according to titration and other criteria. The results of the irradiation experiments are reported in the succeeding paper (cf. Overend and Peacocke, *Trans. Faraday Soc.*, 1950, **46**, 794). The titrations of unirradiated deoxyribonucleic acids confirm Overend and Peacocke's observations that the forward- and the back-titration curves differ greatly from each other. However, a general feature of all the present results has been the separation of the curves obtained on back-titration from pH 2 and pH 12. The validity of this separation is examined below and possible explanations are discussed.

The quantitative analysis of the constituent purines and pyrimidines of nucleic acids has been placed on a firm basis by the application of the methods of paper chromatography to the separation of nucleic acid hydrolysis products (Vischer and Chargaff, *J. Biol. Chem.*, 1948, **176**, 703, 715; Markham and Smith, *Nature*, 1949, **163**, 250; *idem*, *Biochem. J.*, 1949, **45**, 294; Wyatt, *ibid.*, 1951, **48**, 584). The nucleic acids discussed in this paper have been analysed by these methods (Laland, Overend, and Stacey, in the press) and the results enable a more accurate estimate of the proportion of secondary monoester phosphoryl groups to be made from the titration curves than has been possible hitherto. The values calculated imply a greater degree of branching of deoxyribonucleic acids than has been previously assumed.

Titrations of the Sodium Salts of Deoxyribonucleic Acid.—Figs. 1—4 show the titration curves of the sodium salts of deoxyribonucleic acids isolated from calf thymus glands (T_2), herring sperm (H_1), and wheat germ, and of a sample of the sodium salt of calf thymus nucleic acid kindly supplied by Professor Signer of Berne University (for details of the preparation, see Signer and Schwander, *loc. cit.*). Curves I and III throughout refer to the forward titrations with alkali and acid to pH 12 and pH 2, respectively. Curves II and IV refer to the corresponding back titrations from pH 12 and pH 2. The ordinates in the figures represent the number of equivalents of alkali and acid bound by a standard amount of nucleic acid, containing 4 g.-atoms of phosphorus. Below pH 5 and above pH 9 allowance has been made for the added acid and alkali uncombined with the nucleic acid (the " water correction ") by Jordan and Taylor's method (*J.*, 1946, 994). In the calculations of the ionic strength in the titration solution that this method requires, the simplifying assumption was made that each ionised group in the nucleic acid contributed independently to it. This is justified by the experience of protein titrations (Cohn and Edsall, " Proteins, Amino Acids and Peptides," Reinhold Publ. Co., 1943, p. 453; Cannan, Kibrick, and Palmer, *Ann. N.Y. Acad. Sci.*, 1941, **41**, 247) and, since the ionic strength factor differs appreciably from unity only when the water correction is relatively small, this uncertainty does not affect the accuracy of the results over the pH range 3—11. Outside this range, the water correction is relatively large and gives rise to an increasing uncertainty in the value of the ordinate. The size of the circles and of the vertical lines represents the errors caused both by the uncertainty in the ionic strength of the solution and by the error of the pH measurements.

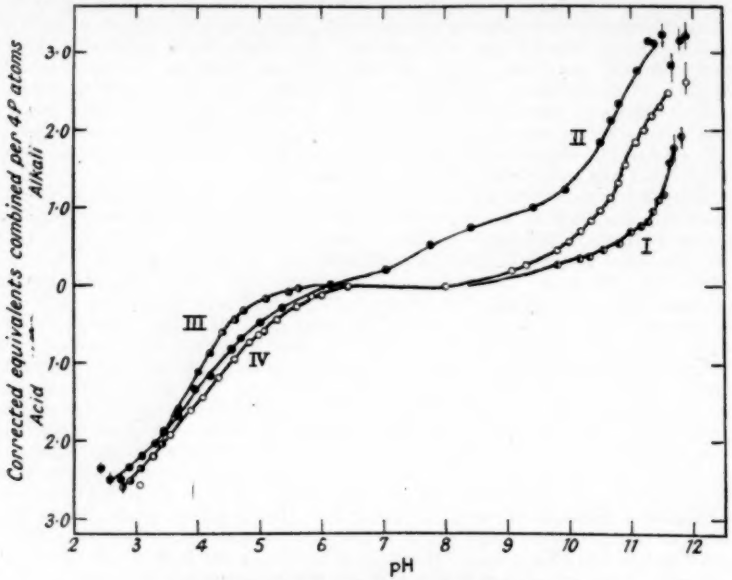
The measured pH values were steady over all the titration range, except in the most alkaline solutions, where there was a tendency for the pH to drop. As carbon dioxide was rigorously excluded in all titrations, this observation was confirmed in separate experiments in which sufficient alkali was added to nucleic acid solutions to bring the pH to 12. In the interval between the 3rd minute after adding alkali and 40 minutes later, the pH of the various solutions decreased by 0·07—0·12 unit.

The results confirm the observations by Gulland, Jordan, and Taylor that in the forward titrations there is a rapid liberation of titratable groups above pH 11 (I) and below pH 5 (III) and that, once liberated, these groups are titratable over the whole pH range (II and IV). The number of groups titrated in the acid region is 2·4—2·8 and in the alkaline region is approximately 2. The separation of the back-titration curves II and IV is a noticeable feature of Figs. 1—4 and is outside the range of the errors already discussed. Curve II implies more alkali or less acid combined with the nucleic acids at a given pH than does IV. The results in Fig. 4 agree with the titration curves of this material already published by Signer and Schwander (*loc. cit.*). Unfortunately in the latter work, II and IV (their curves 2 and 4) were not extended far enough for a test of coincidence to be made.

The sodium salt of a deoxyribonucleic acid isolated from mouse sarcoma by the methods of Mirsky and Pollister (*loc. cit.*) and of Sevag, Lackmann, and Smolens (*loc. cit.*) was also titrated. The relative disposition of the titration curves was identical with those of Figs. 1—4, but,

FIG. 3.

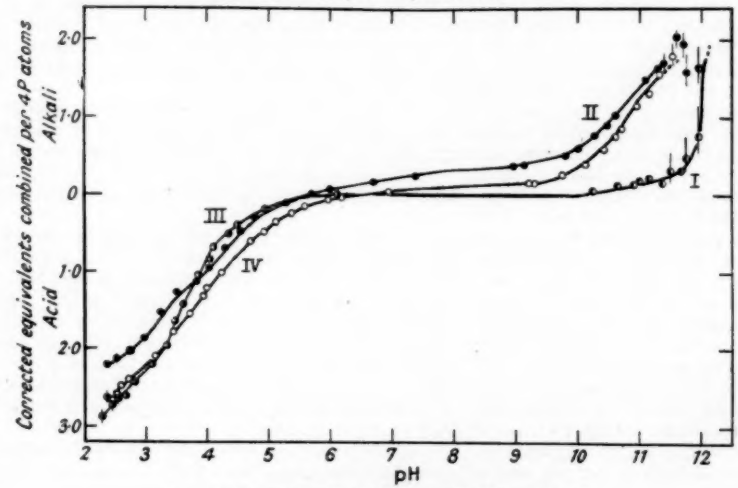
The titration curve of the sodium salt of deoxyribonucleic acid from wheat germ—undried.



◐ I. *Titration with alkali from* pH 6·4 *to* pH 12·0.
● II. *Back-titration with acid from* pH 12·0.
◑ III. *Titration with acid from* pH 6·4 *to* pH 2·4.
○ IV. *Back-titration with alkali from* pH 2·4.

FIG. 4.

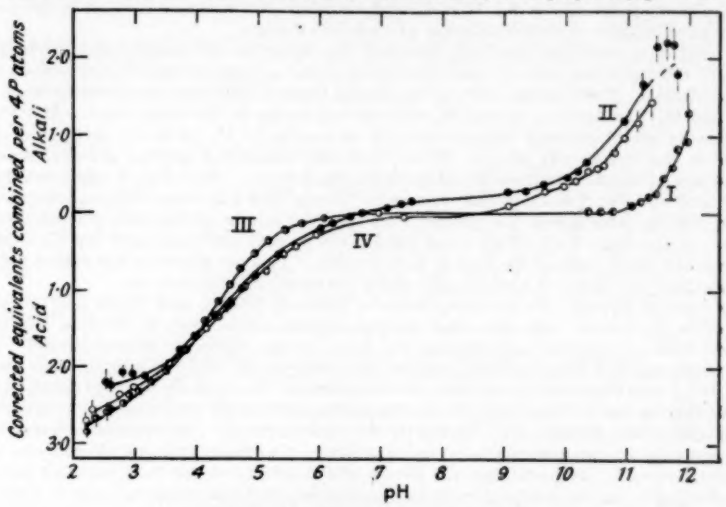
The titration curve of the sodium salt of deoxyribonucleic acid prepared from calf thymus by Signer and Schwander (loc. cit.)*—undried.*



◐ I. *Titration with alkali from* pH 6·1 *to* pH 12·0.
● II. *Back-titration with acid from* pH 12·0.
◑ III. *Titration with acid from* pH 6·1 *to* pH 2·3.
○ IV. *Back-titration with alkali from* pH 2·3.

FIG. 5.

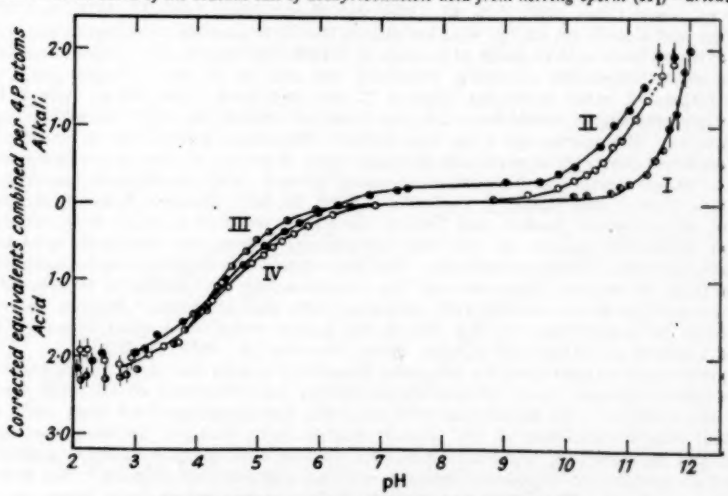
The titration curve of the sodium salt of deoxyribonucleic acid from calf thymus (T_1)—dried.



◐ I. *Titration with alkali from* pH 6·9 *to* pH 12·0.
● II. *Back-titration with acid from* pH 12·0.
◑ III. *Titration with acid from* pH 6·9 *to* pH 2·0.
⊙ IV. *Back-titration with alkali from* pH 2·0.

FIG. 6.

The titration curve of the sodium salt of deoxyribonucleic acid from herring sperm (H_1)—dried.



◐ I. *Titration with alkali from* pH 6·9 *to* pH 12·0.
● II. *Back-titration with acid from* pH 12·0.
◑ III. *Titration with acid from* pH 6·9 *to* pH 2·0.
⊙ IV. *Back-titration with alkali from* pH 2·0.

owing to the high viscosity of the solutions and foaming at alkaline pH, the results above pH 7 are not yet considered sufficiently reliable. Below this pH, the curves are quantitatively very similar to those of Fig. 1. Herring-sperm nucleic acid was also titrated in the presence of potassium chloride (1·0M.) at alkaline pH (see Discussion).

The Effect of Dialysis.—Dialysis, followed by drying in the frozen state, is frequently employed during extractions of deoxyribonucleic acids in order to remove any contaminating sodium chloride. Calf thymus and herring sperm nucleic acids were therefore titrated before (as T_1 and H_1) and after (as T_2 and H_2) dialysis and drying in the frozen state. There was no alteration in the shape and relative position of curves I—IV or in the number of groups titrated in the various pH ranges. There were only minor quantitative differences between the two sets of results and these are of doubtful significance. (N.B. Fig. 1 refers to a dialysed nucleic acid and Fig. 2 to an undialysed acid.) It was shown in other dialysis experiments in sodium chloride solutions of the nucleic acids that the release of inorganic phosphate during dialysis was less than 1·6% of the total phosphorus present and that there was no significant change in the N : P ratio in the nucleic acid solution. Dialysis therefore has only a negligible effect on those properties of nucleic acids which are detectable by titration.

The Effect of Drying.—In the experiments of Gulland, Jordan, and Taylor and of Cosgrove and Jordan, the nucleic acids were dried over phosphoric oxide (110°, 30 minutes, 0·01 mm. of mercury) before dissolution and titration (*loc. cit.*; Jordan, personal communication). In the experiments reported here, however, undried deoxyribonucleic acids containing some moisture (about 15%) were dissolved for titration and the solutions subsequently analysed for phosphorus. The calf thymus and herring sperm deoxyribonucleic acids which were used in our experiments were therefore also titrated after drying by the same method. The titration curves (Figs. 5 and 6) are very similar quantitatively and qualitatively to those obtained after drying by the method mentioned. In particular, the degree of coincidence of the back titration data with acid and alkali is the same, as shown by an examination of the experimental points of the other investigators. Comparison of Figs. 5 and 6 with Figs. 1 and 2 suggests that after the drying the size of the loop formed by I and II and by III and IV is slightly reduced. On the hypothesis already mentioned, this would imply a small reduction in hydrogen bonding caused by drying. The separation of II and IV appears to be greater if the deoxyribonucleic acids are not previously dried.

Discussion.

(a) *Estimation of the Quantity of Secondary Monoester Phosphoryl Groups.*—The work of Simms (*J. Amer. Chem. Soc.*, 1926, **48**, 1239), von Muralt (*ibid.*, 1930, **52**, 3518), and Wyman (see Cohn and Edsall, *op. cit.*, p. 451) has shown that it is possible to represent the titration curve of a polybasic acid in terms of a series of titration constants, G_i'. These constants are the apparent dissociation constants (involving the activity of the hydrogen ion and the concentrations of other molecular species) of the monobasic acids which, mixed in the appropriate proportions, would have the same titration curve as the polybasic substance under consideration. For reasons given by these authors titration constants can be identified with the dissociation constants of particular chemical types of groups, if there is no marked electrostatic or other interaction between dissociating groups. This assumption has frequently been made (Levene and Simms, *J. Biol. Chem.*, 1926, **70**, 327; Fletcher, Gulland, and Jordan, *J.*, 1944, 33; Gulland, Jordan, and Taylor, *loc. cit.*) in order to estimate from nucleic acid titration curves the number of secondary phosphoryl groups, an important quantity not obtainable by direct analytical methods. The procedure is not unambiguous because different combinations of titration constants and the corresponding equivalents of monobasic acids give theoretical titration curves equally coincident with that observed. Another uncertainty arises from the interactions between dissociating groups which must occur in such a highly charged molecule as nucleic acid (Jordan, *Trans. Faraday Soc.*, 1950, **46**, 793).

The error in an estimation of the secondary phosphoryl groups due to the former uncertainty can be greatly reduced when independent analytical determinations of all other titratable groups are available. By chromatographic methods, determinations have been made of the individual constituent bases of the titrated nucleic acids (Laland, Overend, and Stacey, *loc. cit.*) and these give the number of titratable amino-groups, per 4 g.-atoms of nucleic-acid-phosphorus, contributed by guanine, adenine, cytosine, and 5-methyl cytosine. The procedure was then as follows. The titration constants of these amino-groups were taken, as a first approximation, to be similar to the dissociation constants of the same group in the corresponding ribonucleotides, *i.e.*, $pG' = 2·3$, 3·7, and 4·2, respectively (Levene and Simms, *J. Biol. Chem.*, 1925, **65**, 519), since no data on the deoxyribonucleotides are available. The number of

TABLE I.

The titratable groups of the sodium salts of deoxyribonucleic acids.

Source of nucleic acid and treatment before titration:		Calf thymus (undried)		Calf thymus (dried)		Herring sperm (undried)		Herring sperm (dried)		Wheat germ (undried)
Figure:		1	1	5	5	2	2	6	6	3
Curve:		II	IV	II	IV	II	IV	II	IV	IV §
Groups										
1. Amino. Guanine	pG'_1	2·5	2·5	2·5	2·5	2·35	2·35	2·6	2·6	2·9
	Equivs./4P †	0·75	0·75	0·75	0·75	0·71	0·71	0·71	0·71	0·66
2. Amino. Adenine	pG'_2	3·7	3·7	3·85	3·85	3·70	3·70	3·85	3·85	3·85
	Equivs./4P †	1·02	1·02	1·02	1·02	1·0	1·0	1·0	1·0	0·90
3. Amino. Cytosine and 5-methyl cytosine ‡	pG'_3	4·75	4·75	4·85	4·85	4·85	4·85	4·90	4·90	4·5
	Equivs./4P †	0·84	0·84	0·84	0·84	0·92	0·92	0·92	0·92	0·84
4. Secondary phosphoryl groups	pG'_4	7·0	6·5	6·15	6·00	7·00	6·5	6·5	6·5	5·5
	Equivs./4P	0·54	0·33	0·59	0·40	0·28	0·18	0·29	0·27	0·42
5. Enolic hydroxyl groups of guanine and thymine *	Equivs./4P †	1·76	1·76	1·76	1·76	1·76	1·76	1·76	1·76	1·57

* Obtained from analytical data.

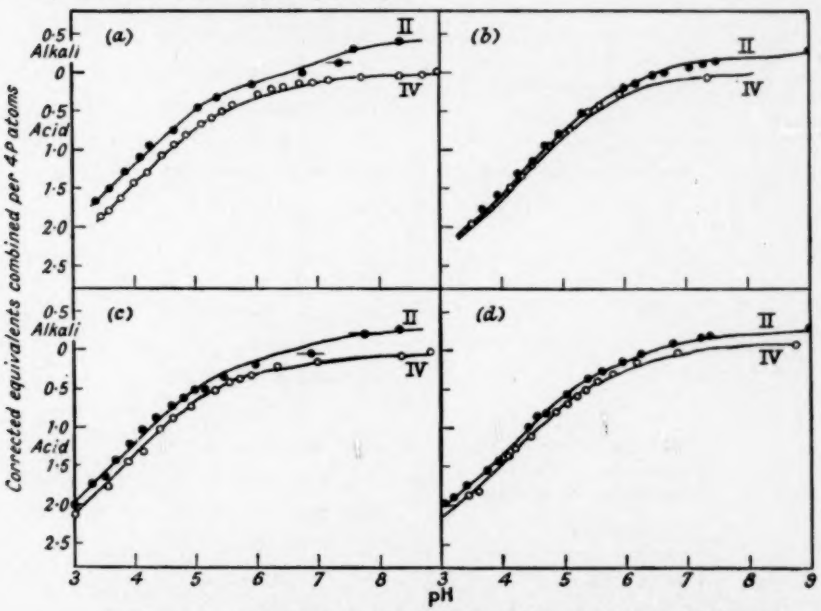
† pG' of amino-group of 5-methylcytosine assumed to be the same as in cytosine.

‡ No pG'_3 given because of the impossibility of representing titration curve above pH 9 by one titration constant only.

§ No detailed analysis was made of curve II for wheat germ nucleic acid, owing to the difficulty of finding a suitable pG'_4 value. The number of secondary phosphoryl groups is high, ~0·6—0·9.

FIG. 7.

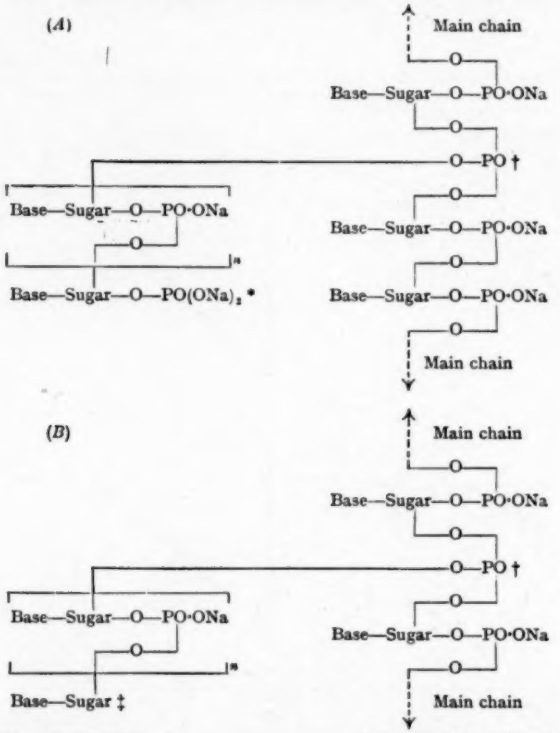
Comparison of calculated titration curves with experimental data. Smooth curves are calculated by using the quantities in Table I and are adjusted in position on the ordinate so as to coincide with the experimental values at the inflexion point (pH 8—9).



Circles are the experimental data from (*a*) Fig. 1; (*b*) Fig. 5; (*c*) Fig. 2; (*d*) Fig. 6.

● II. *Back-titration with acid after alkali treatment.*
⊙ IV. *Back-titration with alkali after acid treatment.*

equivalents of alkali required to titrate such groups from a fixed lower pH, *e.g.*, 3·5, to a fixed higher pH, *e.g.*, 8·5, corresponding to the point of inflexion in the titration, was then calculated by Simms's method (*loc. cit.*) and was invariably less than that experimentally observed. Since no deamination occurs during the titration, this difference must have been due to secondary phosphoryl groups, the only other group dissociating to any appreciable extent in this pH range (pG' = 5·9—7·0; Levene and Simms, *loc. cit.*; Kumler and Eiler, *J. Amer. Chem. Soc.*, 1943, **65**, 2355). By assuming a value of 6—7 for the pG', the number of secondary phosphoryl groups was estimated and the titration curve below the inflexion point was calculated on this basis. If the calculated and observed curves did not have the same shape and curvature, the assumed titration constants were modified and this process of successive approximations was continued until a curve parallel with that observed was obtained. The amount of secondary phosphoryl groups assumed in this last calculation was then the best estimate that could be made from a given experimental curve and had an overall probable error of 0·07 per 4 phosphorus atoms. Alterations in the values taken for the various titration constants were limited by the necessity of obtaining a curve coincident with that observed. The results of the calculations are summarised in Table I, and Fig. 7 shows the theoretical curves and experimental data in the more important cases. It is clear from Fig. 7 that the curves below the inflexion point can be accurately represented as the titration of amino- and secondary phosphoryl groups. The analytically determined numbers of enolic hydroxyl groups (Table I) is in only approximate agreement with the maximum equivalents of base bound (1 and 2), owing to the difficulty of making accurate calculations of the water correction at the highest pH and probably to the presence of a slow reaction with alkali (see below).



* Secondary phosphoryl group. ‡ Sugar with one free hydroxyl group.
† Triesterified phosphoric acid residue — branching point.
Base = adenine, guanine, cytosine, 5-methyl cytosine, or thymine.

Gulland, Jordan, and Taylor (*loc. cit.*), and Cosgrove and Jordan (*loc. cit.*), give 0·25 as the maximum number of secondary phosphoryl groups for every four atoms of phosphorus in calf-thymus and herring-sperm nucleic acids (dried) but considered the actual number to be probably less than this. The number of secondary phosphoryl groups given in Table I are, in general, at least as great as this maximum value and the difference chiefly arises from the assumption by these workers that there were 3·0 amino-groups for every four atoms of phosphorus, whereas the analytical results now show that there are less than this amount, namely 2·61 and 2·63 in the above two nucleic acids [compare the values of 2·60 and 2·64, respectively, found by Wyatt (*loc. cit.*) with these nucleic acids].

(b) *Structure.*—The number of secondary phosphoryl groups calculated from titration curves II and IV can only represent the number of these groups in the units present after alkali and acid treatment, when labile macromolecular linkages which are susceptible to these agents have already been ruptured (see below). However, it is still of interest to enquire into the mode of linking of nucleotides in these units, and, indeed, most discussions of the past have been primarily concerned with them. Since alkali, even under the mild titration conditions, may break some internucleotide linkages (see below), only the numbers of secondary phosphoryl groups deduced from curves IV will be employed in the following discussion. Table I shows that about one in every 10—20 phosphorus atoms possesses a secondary phosphoryl group. These groups cannot be situated solely at the ends of unbranched chains since a degree of polymerisation of only 10—20 nucleotides would not account for the high molecular weights (*e.g.*, $8{\cdot}2 \times 10^5$, Cecil and Ogston, *J.*, 1948, 1382) observed with deoxyribonucleic acids prepared in this way. Branching of the main polynucleotide chain must consequently be occurring, with each branch terminated by a singly esterified phosphoric acid residue. Since the 2-deoxy-D-ribose moiety, unlike the D-ribose in ribonucleic acids, has only two groups (3- and 5-) available for internucleotide linkages (Lythgoe and Brown, *J.*, 1950, 1990), this branching must arise at triply bound phosphorus atoms, as in formula (*A*), which has been written on the assumption that there are no free sugar hydroxyl groups.

The frequency with which branching of the main chain occurs will depend on the number (n) of nucleotides in the side chains and cannot be determined by this type of end-group analysis alone. There is ample evidence that the nucleic acid molecule is extremely asymmetric (*e.g.*, Signer, Caspersson, and Hammarsten, *Nature*, 1938, **141**, 122) and of high molecular weight, so only a negligible proportion of the secondary phosphoryl groups will be those at the end of the long main polynucleotide chain.

The proportions of phosphoric acid residues esterified to different degrees may be calculated from the data of Table I and the ratio of sodium to phosphorus atoms. Of every four phosphorus atoms, let a = the number present as $RO{\cdot}PO(ONa)_2$, the number of secondary phosphoryl groups given in Table I (curves IV); b = the number present as $(RO)_2PO{\cdot}ONa$; and c = number present as $(RO)_3PO$, where R = a nucleoside residue. By definition, $(a + b + c) = 4$. Also, since the nucleic acid is isolated at pH 6—7 in the presence of sodium chloride only, all the primary and secondary phosphoryl groups will be present in their charged form (see curves III), combined with sodium. So, $b = (d - 2a)$, where d is the number of sodium atoms for every 4 phosphorus atoms, by analysis. The two equations enable b and c to be calculated (Table II).

TABLE II.

Proportions of different phosphoryl linkages in the sodium salts of deoxyribonucleic acids.

Source of deoxyribonucleic acid and treatment before titration :		Calf thymus (undried)	Calf thymus (dried)	Herring sperm (undried)	Herring sperm (dried)	Wheat germ (undried)
$RO{\cdot}PO(ONa)_2$	a =	0·33 ± 0·07	0·40 ± 0·07	0·18 ± 0·07	0·27 ± 0·07	0·42 ± 0·07
$(RO)_2PO{\cdot}ONa$	b =	3·34 ± 0·16	3·20 ± 0·16	2·84 ± 0·16	2·66 ± 0·16	3·16 ± 0·21
$(RO)_3PO$	c =	0·33 ± 0·17	0·40 ± 0·17	0·98 ± 0·17	1·07 ± 0·17	0·42 ± 0·22
P atoms without corresponding base molecules (by analysis) *		0·38 ± 0·07	0·38 ± 0·07	0·32 ± 0·07	0·32 ± 0·07	0·69 ± 0·07

All figures are calculated for 4 phosphorus atoms.
The probable errors of b and c are high because of the cumulative effect of the calculations.
* Cf. Wyatt, *loc. cit.*

In calf-thymus and wheat-germ deoxyribonucleic acid, a and c are equal and, within the error limits of the method, are also approximately equal to the number of phosphorus atoms without corresponding molecules of base. This is in accordance with (*A*) as the only mode of

branching of the polynucleotide chain. However, in herring sperm nucleic acid, *a* is approximately equal, within the limits of error, to the number of phosphorus atoms with no corresponding molecules of base but both of these figures appear to be significantly less than *c*, because the sodium : phosphorus ratio is less than unity. This implies that a significant number of the triply bound phosphorus atoms in this nucleic acid are linked indirectly to a base molecule but not to a secondary phosphoryl group. This could arise from the occurrence of structures such as (*B*), as well as (*A*), in this sample of herring sperm nucleic acid. In (*B*) there is a free sugar hydroxyl group and, in accordance with this and in contrast with thymus nucleic acid (Gulland, Jordan, and Taylor, *loc. cit.*, Fig. 2, curve III), the titration curve of this herring sperm nucleic acid at pH 12 in 1·0M-potassium chloride (to reduce water-correction errors) showed no inflexion point, which would have appeared if free sugar hydroxyl groups were not being titrated.

(c) *The Back-titration Curves.*—The separation of the back titration curves II and IV has been observed by us in altogether 14 independent titrations of the deoxyribonucleic acids from the sources mentioned. This feature of the titration curve is less noticeable if the nucleic acids are dried before titration, and the view of Gulland, Jordan, and Taylor (*loc. cit.*) that these curves are virtually coincident may be due to a difference in technique of this type. Three types of explanation of the difference can be suggested.

(i) The investigations of Cannan, Kibrick, and Palmer (*loc. cit.*; *J. Biol. Chem.*, 1942, **142**, 803) and of Cohn, Green, and Blanchard (*J. Amer. Chem. Soc.*, 1937, **59**, 509) have shown that increasing the salt concentration causes the titration curves of proteins to rotate around their isoelectric points. Solutions alkaline to this point, the case corresponding to nucleic acid titrations above pH 2·0—2·5, become more acid on the addition of salt and the effect is greater the more negative the charge. Since no attempt has been made to maintain the ionic strength constant during the titrations the possibility arises that variations in ionic strength may have been sufficient in magnitude and sign to cause the difference observed between II and IV.

The calculation of the total ionic strength of a titration mixture at each pH has already been discussed; it is never found to vary by more than 0·005 unit over the full course of the titrations. When the titration is continued for any length of time there is a danger of diffusion of potassium chloride from the end of the saturated salt bridge. This would cause the ionic strength at the end of curves II and IV to be greater than at the beginning by an amount not exceeding 0·03 unit, as determined by experiment. Detailed examination shows that if one allows for this effect, back-titration curves from pH 12 and 2·5 are obtained to replace II and IV which are, if anything, separated more than before, so that other explanations must be sought.

(ii) Gulland, Jordan, and Taylor suggested that the hydrogen bonds in these nucleic acids were ruptured with equal facility by acid and alkali and that they linked two groups, one of which titrated in the acid region and the other in the alkaline region, *e.g.*, the amino-groups and the titratable $-NH-C=O \rightleftharpoons -N=C-OH$ systems of guanine and thymine, respectively. The presence of such bonds can still be regarded as a satisfactory explanation of the major part of the difference between the forward- and the back-titration curves presented here. If, in addition, there were also present smaller numbers of hydrogen bonds which could be broken only by acid or by alkali, then the two back-titration curves would not be coincident: each would represent the titration of nucleic acid molecules with different residual hydrogen bonding. Such hydrogen bonds would have to link groups titrated in the acid range or in the alkaline range to other groups not dissociating during the titration (*e.g.*, primary phosphoryl groups). Some evidence for the existence of these two types of hydrogen bond in deoxyribonucleic acids is available.

After ultrasonic irradiation of herring-sperm nucleic acid the difference between III and IV disappears but continued irradiation, long after the viscosity has ceased to fall, never entirely eliminates the difference between I and II and between I and IV (unpublished work). It appears that hydrogen bonds are present which are broken only by alkali treatment but do not affect titration at acid pH values. Similar curves have been obtained by Gulland, Jordan, and Taylor (*loc. cit.*, Figs. 6, 4, and 5) with certain samples of thymus nucleic acid. More recently, Cavalieri and Angelos (*J. Amer. Chem. Soc.*, 1950, **72**, 4686) have shown that treatment of thymus nucleic acid with acid or alkali (pH 3 and 12) greatly increased the number of primary and secondary phosphoryl groups available for the binding of the cationic dye, rosaniline. These authors therefore postulate that the phosphoryl groups are linked by hydrogen bonds to amino-groups and, we would add, to enolic hydroxyl groups also. It is of interest that alkali and acid treatment were not equally effective in releasing primary phosphoryl

anions and this would support the postulate of two types of hydrogen bond involving primary phosphoryl groups.

This explanation of the separation of II and IV therefore seems to have a reasonable basis and was that previously put forward (Overend and Peacocke, *Trans. Faraday Soc.*, 1950, **46**, 783). However, it has subsequently been shown (following paper) that, although ultrasonic irradiation breaks down almost all of the hydrogen bonding of herring sperm nucleic acid, the separation of II and IV is as great as in the unirradiated sample. Also on this hypothesis and contrary to the evidence of Figs. 1—6, II and IV should become coincident over the pH ranges (about 8) where no groups are being titrated. This implies that some factor other than hydrogen bonding may be chiefly responsible for the separation of II and IV.

(iii) If, in addition to rupture of the hydrogen bonds responsible for the distinction between forward- and back-titration curves, there was also an irreversible neutralisation of acid and alkali, then II would be displaced upwards and IV downwards, causing a separation of the kind observed. Preliminary evidence for such a reaction with alkali is provided by the observed tendency for the pH to decrease slightly in very alkaline solutions; with acid, however, the pH values were quite stable, even in the most acid solutions. No ammonia was detected in alkaline nucleic acid solutions under the titration conditions, so no hydrolysis of amino-groups can have occurred.

Euler and Fonó (*Arkiv Kemi, Min., Geol.*, 1948, **25**, No. 3) have reported that treatment of thymus nucleic acid with alkali at pH 11·4 and 25° caused a release of secondary phosphoryl groups, amounting to 0·9 per 4 phosphorus atoms in 330 minutes. They suggested that the alkali ruptures ester linkages between secondary phosphoryl and enolic hydroxyl groups, but no titration evidence for release of the latter groups was presented. A kinetic analysis by ourselves of their plot of secondary phosphoryl groups formed against hydrolysis time shows that the initial release of groups was at first very rapid (0·36 group/4P at a first-order rate constant of ~1 min.$^{-1}$). This was followed by a slower release of 0·27 group at a first-order rate constant of $5{\cdot}1 \times 10^{-2}$ min.$^{-1}$, and a further 0·27 group at $3{\cdot}0 \times 10^{-3}$ min.$^{-1}$. The initial fast reaction may consist of the breakdown of both hydrogen bonds involving secondary phosphoryl groups, thereby bringing their p*G'* into Euler and Fonó's titration range (pH 5—8), and of labile $C_{(1)}$-phosphate linkages, as discussed below. In the slower reactions with alkali some of the internucleotide linkages must be ruptured in order to form such a high proportion of secondary phosphoryl groups.

The occurrence, under the very similar conditions (pH 12, 25°, 10—20 minutes) of our titration experiments, of similar reactions with alkali would explain both the separation of II and IV and the greater quantity (about 0·1—0·2 by Table I) of secondary phosphoryl groups apparently present after alkali treatment as compared with acid treatment. The separation of II and IV below pH 6 could be caused by the presence, in alkali treated nucleic acid, of extra acidic groups not titrated at pH 2—12, such as primary phosphoryl groups. These could only arise from the hydrolysis by alkali of one of the linkages of triesterified phosphoric acid residues (see *A* and *B*). In this explanation of the curves, the dried nucleic acids must be assumed to be rather more stable towards these various effects of alkali. The sedimentation-constant measurements by Cecil and Ogston (*loc. cit.*) on thymus nucleic acid further support this view of the effect of acid and alkali. Acid treatment (pH 3·5, room temperature) caused some disaggregation and these changes proceeded to a limit, apparently after only 10 minutes' treatment. Alkali treatment (pH 12·5, room temperature), however, caused a progressive and more profound disaggregation, ultimately producing particles too small to sediment. Cavalieri and Angelos (*loc. cit.*, footnote, p. 4690) also noted variations in the behaviour of thymus nucleic acid with different times of exposure to alkali.

It is not possible to decide between explanations (ii) and (iii) from the titration curves alone, by observing if II and IV coincide with each other at the extremes of pH or continue parallel, since the errors are too great in these regions of the curves. Both factors may be involved in the separation of II and IV, although the available evidence suggests that the occurrence of an irreversible reaction is chiefly responsible.

(d) *Labile Linkages.*—The suggestion has been made made (Stacey, Li, and Overend, *Nature*, 1949, **163**, 538; Overend, Stacey, and Webb, forthcoming publication) that a small proportion of the $C_{(1)}$ atoms of 2-deoxy-D-ribose in nucleic acids may be involved in highly labile, polymeric linkages, possibly with phosphoric acid residues, as well as in glycofuranosidic linkages to the bases. Even at 25°, such a linkage would be very labile to acids (Friedkin, *J. Biol. Chem.*, 1950, **184**, 449) and to alkali (Cori, Colowick, and Cori, *J. Biol. Chem.*, 1937, **121**, 465; Farrar, *J.*, 1949, 3131; Foster, Overend, and Stacey, *J.*, 1951, in the press). Complete and rapid

hydrolysis of these bonds should therefore occur with acid and alkali, releasing free phosphoryl groups and the $\geqslant C_{(1)}\cdot OH$ group of the sugar, which would be in equilibrium with detectable quantities of the straight-chain *aldehydo*-form (Overend, *J.*, 1950, 2769). Evidence will be presented elsewhere that acid and alkali under the titration conditions do in fact release aldehyde groups by very fast reactions. These reactions, like the rupture of hydrogen bonds between amino- and enolic hydroxyl groups, would cause no difference between II and IV.

The *N*-glycosidic bond between 2-deoxy-D-ribose and the purine bases is known to be unstable in acid solution but it has recently been shown (Volkin, Khym, and Cohn, *J. Amer. Chem. Soc.*, 1951, **73**, 1533) that the deoxyribose analogue of adenylic acid is converted into adenine at the rate of only 2% per hour in 0·01N-hydrochloric acid at room temperature. Hence only negligible hydrolysis of this bond would be expected to occur during the titrations at low pH.

(e) *The Dissociation of Deoxyribonucleic Acids.*—The dissociation of long-chain polybasic acids has attracted increasing attention in recent years (Overbeek, *Bull. Soc. chim. Belg.*, 1948, **57**, 252; Katchalsky, Künzle, and Kuhn, *J. Polymer Sci.*, 1950, **5**, 283; Wall and de Butts, *J. Chem. Physics*, 1949, **17**, 1330) and experimental data on synthetic charged polymers of this type are accumulating (Katchalsky and Spitnik, *J. Polymer Sci.*, 1947, **2**, 432; Arnold and Overbeek, *Rec. Trav. chim.*, 1950, **69**, 192). Qualitatively, one of the main results of this work is that the apparent dissociation constant (pK') of a group is strongly dependent on the concentration and charge of the polybasic acid and on the ionic strength of the solution. The theoretical work of Overbeek (*loc. cit.*, Fig. 1) and the experiments of Arnold and Overbeek (*loc. cit.*, Fig. 1) show that, when the change in shape with varying charge is also taken into account, the pK' of an acidic group may increase steadily with molecular charge (*i.e.*, decreasing acidic strength), or increase at first and then slowly decrease again, according to the ionic strength.

The pK' values (= pG', because no other groups are being titrated in this region) of the enolic hydroxyl groups in the present nucleic acid titrations above pH 9, when the negative charge on the molecule is relatively large, show an initial increase and then decrease slightly again (cf. Jordan, *loc. cit.*, 1950). The decrease, however, occurs in the pH region above 11 where the experimental data are least precise. An exact comparison of these results with published theoretical predictions is not possible but they indicate that titrations of nucleic acids under conditions of controlled ionic strength should yield useful information about the degree to which nucleic acids may be represented by various theoretical molecular models. Because of this variation of dissociation constant, and hence of titration constant, with pH too much weight must not be attached to the titration constants in Table I; they can only represent average values for each group over certain pH ranges.

It is hoped to isolate sufficiently large quantities of deoxyribonucleic acids to extend this work to titrations at controlled ionic strengths in order to provide data for comparisons with theory and for a more quantitative study of the importance of the various explanations of the back-titration curves. Eventually such data will also be important in analyses of the effect of ionic strength on viscosity and in studies on the importance of hydrogen bonding in the macromolecular structure of these nucleic acids.

Experimental.

Preparation of the Sodium Salts of the Deoxyribonucleic Acids.—Nucleic acid (T_1) from thymus gland was prepared by a combination of the methods of Mirsky and Pollister (*loc. cit.*) and of Sevag, Lackmann, and Smolens (*loc. cit.*). The nucleic acid was precipitated from saline solutions by the addition of ethanol, washed with 90% ethanol to remove salts, and dried in a desiccator.

Nucleic acid (H_1) from soft herring roe was obtained from a solution of nucleoprotein, isolated by the method of Mirsky and Pollister (*loc. cit.*), by precipitation of the protein with excess of sodium chloride, centrifugation, and precipitation of the nucleic acid by the addition of ethanol. The nucleic acid was washed with 90% ethanol to remove salts and dried in a desiccator.

Full details of the isolations of T_1 and H_1 nucleic acids, which were carried out by Mr. S. G. Laland, will subsequently be published.

A second sample of nucleic acid from thymus gland (T_2), was prepared by dissolving T_1 (178 mg.) in distilled water (18 ml.) and dialysing it against distilled water (285 ml.) at room temperature for 28 hours. The resulting sample was dried in the frozen state, yielding 140 mg. of material.

A second sample of nucleic acid (H_2), from soft herring roe, was obtained by dissolving sample H_1 (500 mg.) in distilled water (50 ml.), and dialysing it for 28 hours against distilled water (600 ml.) at room temperature. The resulting solution was dried in the frozen state.

Nucleic acid from wheat germ was isolated as described by Laland, Overend, and Webb (*Acta Chem. Scand.*, 1950, **4**, 885).

Composition of the Sodium Salts of the Deoxyribonucleic Acids.—Before analysis, the samples were dried over phosphoric oxide at 110°/0·02 mm. The samples were analysed by Mr. S. G. Laland with the exception of the sodium to phosphorus ratio analysis. Full details of the methods used will be published. Results are recorded in the tables.

Determination of Sodium.—The sodium salt of the deoxyribonucleic acid (20 mg.) was digested with concentrated sulphuric acid (0·3 ml.) in a Pyrex micro-Kjeldahl flask until completely charred, and then carbonaceous material was oxidised to yield a clear solution by the addition of concentrated nitric acid (2 drops). Heating was continued until no more nitric acid fumes were evolved and the solutions were transferred to platinum crucibles. Water and sulphuric acid were removed by heating over a steam-bath and then over a small flame.

The remainder of the analysis was continued according to the methods of Overman and Garrett (*Ind. Eng. Chem.*, 1937, **9**, 72) for the removal of phosphorus and of Barber and Kolthoff (*J. Amer. Chem. Soc.*, 1928, **50**, 1625) for the determination of sodium.

Titration Procedure.—Solutions were prepared by dissolving air-dry samples in boiled distilled water and analysed for phosphorus as described by Jones, Lee, and Peacocke (*J.*, 1951, 623). The titrations were performed in an atmosphere of nitrogen at 25°, the gas serving both to stir the solutions and to keep them free from carbon dioxide. pH measurements were made with a Cambridge pH meter in conjunction with Cambridge glass electrodes (" Alki " electrodes above pH 9) and a saturated calomel electrode. Electrical contact between the latter and the titrated solution was maintained by a saturated potassium chloride salt bridge.

For the purpose of standardising the pH meter, 0·05M-sodium borate and 0·05M-potassium hydrogen phthalate were assumed to have pH 9·18 and 4·008, respectively. This pH scale is the " saturated calomel scale " of Hitchcock and Taylor (*J. Amer. Chem. Soc.*, 1937, **59**, 1812) and is recommended by Harned and Owen (" The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., 1943, p. 320). The error in the measurement of pH was ±0·01 unit at all pH values.

	N, %	P, %	N/P, %	Na/P (atoms)	Sodium ribonucleate, %	$\lambda_{max.}$ (mμ) †	η (rel.) ‡
T_1 and T_2	12·8	7·90	1·62	1·0 *	1·3	259	3·6
H_1 and H_2	13·40	8·35	1·61	0·80 ± 0·02	0·4	259	1·85
Wheat germ sample	13·70	8·65	1·59	1·00 ± 0·04	4·80	259	1·33

* One estimation only (Gulland, Jordan, and Taylor give the same figure; ratio in Signer and Schwander's thymus nucleic acid, found by us, is 0·98).

† Wave-length of maximum ultra-violet absorption.

‡ Viscosity relative to water measured at 25° in an Ostwald viscometer at a concentration of 0·05%.

	Moles of adenine/4P	Moles of guanine/4P	Moles of cytosine/4P	Moles of 5-methyl-cytosine/4P	Moles of thymine/4P
T_1 and T_2	1·02	0·75	0·78	0·07	1·01
H_1 and H_2	1·0	0·71	0·82	0·10	1·05
Wheat germ sample ...	0·90	0·66	0·65	0·19	0·91

0·05N- and 0·10N-Hydrochloric acid and potassium hydroxide were used to titrate solutions of initial volume 7—10 ml.

In order to determine the water correction, blank titrations against water of the acid and base used were performed as above.

Release of Phosphorus during the Dialysis of Nucleic Acids.—A solution of the sodium salt of thymus nucleic acid (T_1), containing sodium chloride (1·66M.), was analysed for nitrogen and phosphorus by the methods of Allen (*Biochem. J.*, 1940, **34**, 858) and of Ma and Zuazaga (*Ind. Eng. Chem., Anal.*, 1942, **14**, 280) respectively. The solution was dialysed at room temperature in cellophane tubes against running tap water until free from salts (1475 minutes) and then analysed as above. Dialysis caused only a 1% change in the N : P ratios and there was no significant change in pH.

In a further experiment a solution of the sodium salt of herring-roe nucleic acid, H_1 (200 mg.) in 1M-sodium chloride (125 ml.) was dialysed against distilled water (190 ml.), at room temperature. The dialysate was replaced by distilled water every 24 hours until free from sodium chloride. Phosphorus analysis of the combined dialysates showed that less than 1·6% of the total nucleic acid phosphorus originally present was released during the dialysis.

Release of Ammonia from Nucleic Acid Solutions at pH 12.—Potassium hydroxide solution (0·05M.) was added to a solution of nucleic acid (5 mg./ml.), until the pH was 12. Nitrogen was passed through the solution into Nessler's reagent, which remained unchanged in colour even after 30 minutes. Nucleic acid was shown not to interfere with the release of ammonia from the solution by adding ammonium chloride. Less than 0·1% of the nitrogen in the nucleic acid would have been detected by this method had it been released as ammonia.

It is a pleasure to acknowledge the helpful discussions and interest of Professor M. Stacey, F.R.S., and Dr. W. G. Overend. Part of the costs of this research was defrayed by Imperial Chemical Industries Limited and by the British Empire Cancer Campaign (Birmingham Branch), and one of us (W. A. L.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant.

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[*Received, June 5th*, 1951.]

743. *The Electrometric Titration of the Sodium Salts of Deoxyribonucleic Acids. Part II.* The Effect of Ultrasonic Irradiation.*

By W. A. Lee and A. R. Peacocke.

The effects of ultrasonic irradiation on the titration curves of the sodium salt of the deoxyribonucleic acid of herring sperm have been studied. In the degraded product the difference between forward- and back-titration curves is greatly decreased, although the separation of the two back-titration curves still persists (see Part I *). There is an increase in the number of secondary phosphoryl groups and probably also in the number of primary phosphoryl groups. Ultrasonic waves cause a breakdown of hydrogen bonding and rupture of some internucleotide linkages.

It has been observed that high-frequency sound waves lower the viscosity and degrade both natural and synthetic polymers (Szent-Gyorgi, *Nature*, 1933, **131**, 278; Schmid and Rommel, *Z. physikal. Chem.*, 1940, *A*, **185**, 98; Melville and Murray, *Trans. Faraday Soc.*, 1950, **46**, 996). Recent work in this laboratory (Laland, Overend, and Stacey, *Research*, 1950, 386) and the investigation by Goldstein and Stern (*J. Polymer Sci.*, 1950, **5**, 687) have shown that deoxyribonucleic acids are similarly degraded by ultrasonic irradiation.

Laland, Overend, and Stacey (*loc. cit.*; also forthcoming publication) showed that ultrasonic irradiation of deoxyribonucleic acids, isolated from calf thymus glands, from soft herring roes, and from wheat germ, resulted in a rapid fall in viscosity which was not regained on storage but continued to fall slightly. During irradiation no purine or pyrimidine bases were liberated and only negligible amounts of inorganic phosphate and ammonia were formed. The products were still insoluble in acid and ethanol, but the structural viscosity and streaming birefringence of the original nucleic acid had disappeared. These and other physical measurements indicated that disaggregation had occurred but that the products were still of relatively high molecular weight, and this is confirmed by the sedimentation-constant measurements by Goldstein and Stern (*loc. cit.*).

Since certain features of the titration curves of nucleic acids can be explained by postulating various weak polymeric linkages (Part I, *loc. cit.*) likely to be susceptible to ultrasonic waves, the changes in the titration curves of herring sperm deoxyribonucleic acid degraded to different degrees by ultrasonic irradiation have been examined (for preliminary report see Overend and Peacocke, *Trans. Faraday Soc.*, 1950, **46**, 794). The results help to elucidate the nature of the breakdown due to the irradiation, and also confirm that the difference between forward- and back-titration curves, described in Part I, is closely associated with the existence of polymeric linkages, such as hydrogen bonds. That the separation of the curves obtained by back-titration with acid and alkali is hardly altered by ultrasonic degradation supports the hypothesis (see Part I) that this separation is due to an irreversible neutralisation of the alkali.

Titration Curves.—Figs. 1—3 show the titration curves of samples of the sodium salt of herring sperm deoxyribonucleic acid which have been isolated from solutions of the nucleic acid after various periods of ultrasonic irradiation. The irradiation was carried out at atmospheric pressure and under these conditions cavitation should occur, producing the maximum rate of depolymerisation. These figures should be compared with the titration curves of the same nucleic acid before irradiation (Fig. 2, Part I); the same Roman numerals are used to designate the various forward- and back-titration curves and the ordinate represents the same quantity as in the figures of Part I.

The main features of these titration curves are as follows. (*a*) As irradiation continues, the forward-titration curves approach the corresponding back-titration curves, and in the acid range the curves III and IV become almost coincident (Fig. 3). The area enclosed by the forward and back-titration curves is a measure of their relative displacement; the changes in these areas are given in Table I. Since certain reactions with alkali seem to affect the position of curve II (see Part I), the change is most clearly seen with curves III and IV. Unlike III and IV, curves I and II never become completely coincident, and a possible interpretation of this has already been discussed (Part I).

(*b*) The solutions given by irradiated nucleic acid samples were all of lower pH ($\simeq$5·5) than that given by the unirradiated nucleic acid (6·9). This indicates that some acidic group has been liberated. Goldstein and Stern (*loc. cit.*) observed no change in pH on irradiation for

* Part I, preceding paper.

TABLE I.

Ultrasonic irradiation time (mins.)	0	95	180	270
Area * enclosed by I and II	5·2	4·1	2·3	—
Area * enclosed by III and IV	3·0	1·7	1·4	0·2
Estimate † of increase in primary phosphoryl groups/4P { By II	—	0·12	0·12	0·20
{ By IV	—	0·12	0·20	0·18
Estimate † of increase in secondary phosphoryl groups/4P { By II	—	0·20	0·16	0·36
{ By IV	—	0·20	0·20	0·32
Total number of ‡ $(RO)_2PO{\cdot}ONa$ groups. By IV	2·84	2·44	2·44	2·20
Total number of secondary phosphoryl groups/4P. By IV	0·18	0·38	0·38	0·50
η (rel.) (25°) of nucleic acid solution before freeze-drying	5·8—6·5	1·8	1·33	1·21

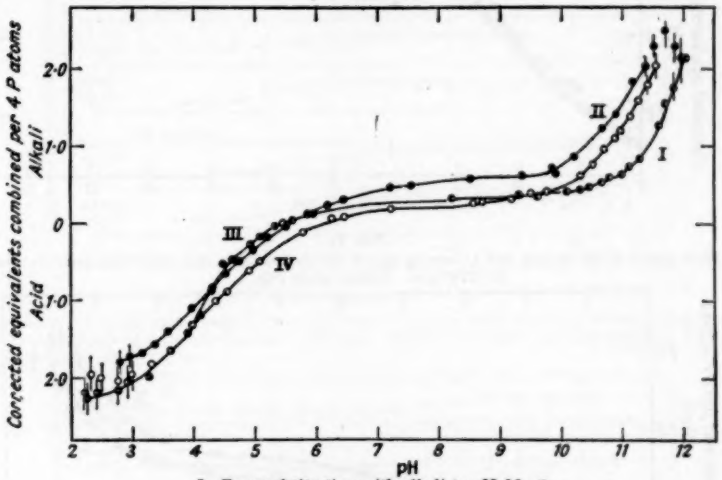
* Unit of area = rectangle formed by 1 unit on abscissa and 1 unit on ordinate of Fig. 1—3.

† The increase in the number of secondary phosphoryl groups is accurate only to within ± 0·06, and the increase in the primary groups is even less precisely measurable since it is sensitive not only to the error in each individual measurement but also to the absolute reproducibility of the curves.

‡ R = Nucleoside residue: calculated as *b* in Table II, Part I.

FIG. 1.

Titration curves of the sodium salt of herring sperm deoxyribonucleic acid after ultrasonic irradiation for 95 mins.



I. Forward-titration with alkali to pH 12, ◐.
II. Back-titration with acid from pH 12, ●.
III. Forward-titration with acid to pH 2, ◑.
IV. Back-titration with alkali from pH 2, ○.

periods of 25 minutes. The difference is probably caused by the much longer irradiation times employed in these experiments.

(*c*) Over the pH range 5—6, the titration curves of unirradiated nucleic acids rise more steeply than before irradiation. This characteristic of the curves is illustrated more precisely by Fig. 4, where a given curve, *e.g.*, II, of the unirradiated nucleic acid is compared with the corresponding curve (II) of an irradiated sample in order to eliminate the various effects of acid and alkali; the curves in Fig. 4 then represent changes due to the irradiation. The irradiation has caused an increase in the number of groups titrated over the pH range 5—6. Ammonia is formed in only negligible quantities by extended irradiation (Laland *et al.*, *loc. cit.*), so no deamination, with the appearance of xanthine hydroxyl groups ($pK' = 6{\cdot}0$ in xanthosine; Ogston, *J.*, 1935, 1376), can have occurred. The only other known groups dissociating near this region are the amino-groups of cytosine (dissociation constant in the ribonucleotide = 4·2; titration constant according to the analysis of Part I ≃4·85), and secondary phosphoryl groups (dissociation constants reported vary from 5·9 to 7·0 in ribonucleotides and sugar phosphates; for references see Part I). All the amino-groups of the bases, determined analytically, are free and titratable in curves II and IV obtained with the original nucleic acid (see Part I, where

the analytical figures for amino-groups can fully account for the titration curve in the acid region). The amino-groups are therefore not involved in any main covalent linkage in the unirradiated acid and there seems to be no possibility of an increase in their number. Finally,

FIG. 2.

Titration curves of the sodium salt of herring sperm deoxyribonucleic acid after ultrasonic irradiation for 180 min. Curves as in Fig. 1.

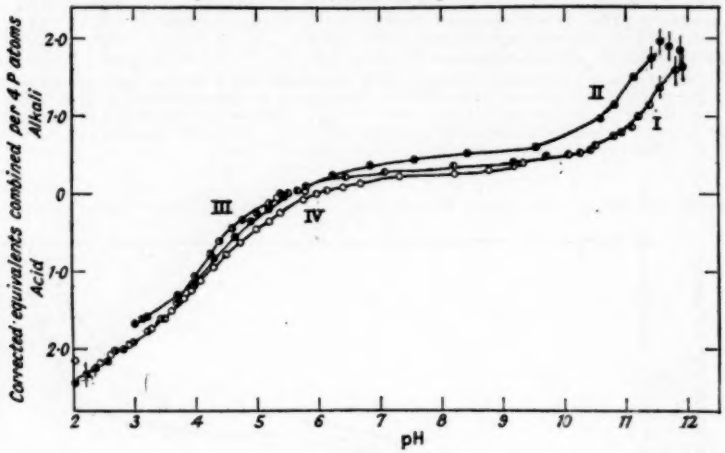
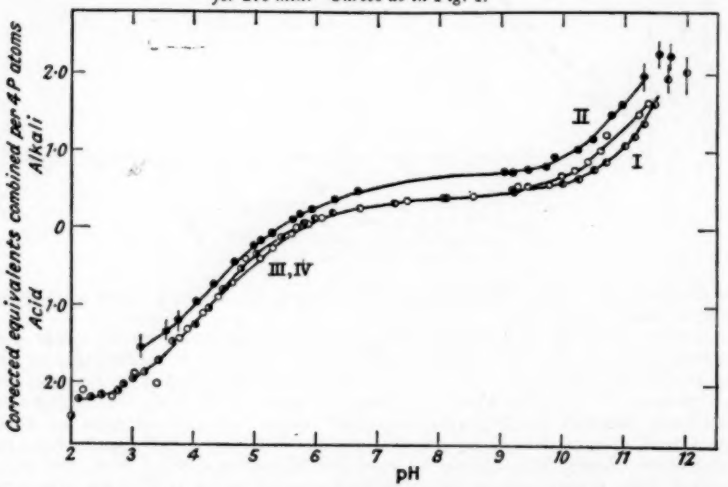


FIG. 3.

Titration curves of the sodium salt of herring sperm deoxyribonucleic acid after ultrasonic irradiation for 270 min. Curves as in Fig. 1.



any increase in the number of amino-groups would tend to increase the pH of the solution, not to decrease it, as observed. The extra groups formed which are titrated in the pH range 5—6 can therefore be identified as secondary phosphoryl groups.

The ordinate in Fig. 4 is finite and positive below pH 4, so the increase in the acidity of nucleic acid solutions after irradiation also seems to be partly caused by formation of acidic groups not titrated over the pH range (2—12) of the experiments. The only possible acidic group

fulfilling such conditions is the primary phosphoryl group. Table I records the approximate increase in the number of the two types of phosphoryl group. The figures for 270 minutes' irradiation indicate that even at this point, long after the viscosity has ceased to fall, secondary phosphoryl groups are still being formed.

(*d*) The separation of the back-titration curves II and IV, discussed in Part I, is also observed in these experiments, and Fig. 5 shows that it is very little affected by ultrasonic irradiation. This contrasts with the effect of irradiation on the displacement of a forward-titration curve

FIG. 4.

The effect of ultrasonic irradiation for various periods on the back-titration curves of the sodium salt o herring sperm deoxyribonucleic acid: difference between curves obtained on back-titration with alkali from pH 2, ○; *difference between curves obtained on back-titration with acid from* pH 12, ●.

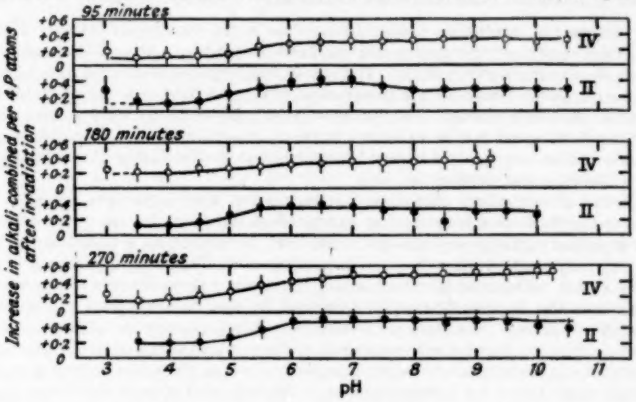
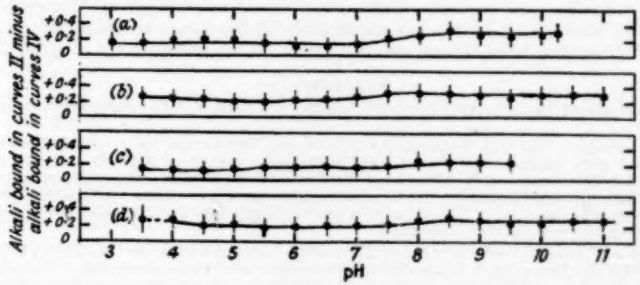


FIG. 5.

Difference between the two back-titration curves (II and IV) of the sodium salt of herring sperm deoxyribonucleic acid before and after ultrasonic irradiation. Irradiation time: (a) *Unirradiated*; (b) 95 *min.*; (c) 180 *min.*; (d) 270 *min.*



from the corresponding back-titration curve and different explanations of the two sets of observations are necessary (see Part I).

DISCUSSION.

The general conclusions of Laland, Overend, and Stacey (*loc. cit.*) are confirmed by the titration data presented here, since the main pattern of the curves is preserved and there is no major alteration in the number of groups titrated, excluding the phosphoryl groups. The titration data suggest two main effects of ultrasonic irradiation on deoxyribonucleic acids. First, the weaker bonds, which are responsible for the difference between forward- and back-titrations and are broken by mild acid or alkali treatment, are also gradually broken by continued irradiation. Gulland, Jordan, and Taylor (*J.*, 1947, 1131) and Creeth, Gulland, and Jordan (*ibid.*, p. 1141) have suggested that these weaker linkages are hydrogen bonds, cross-linking

groups in various polynucleotide chains, and that they are also responsible for the high structural viscosity of nucleic acid solutions. This suggestion is supported by the present work, which shows that ultrasonic irradiation decreases the displacement of the forward- from the back-titration curves and at the same time reduces the viscosity, incidentally destroying its structural character. The trends in these quantities as irradiation continues are expressed relatively to their initial values for the unirradiated nucleic acid in Table II. The viscosity is seen to decrease relatively faster than does the area enclosed by I and II and by III and IV.

TABLE II.

Time of irradiation (mins.)	0	95	180	270
Relative area enclosed by I and II	100	79	38—58	—
Relative area enclosed by III and IV	100	57	47	7
η (rel.) (25°) as % of original value before each irradiation	100·0	25·6	22·9	20·9

Secondly, ultrasonic irradiation causes an increase in the number of primary and secondary phosphoryl groups, and the latter groups are still being formed even after 270 minutes' irradiation, when the viscosity is altering very little. Groups of this type could only be formed by a gradual rupture of internucleotide linkages which are of a very much higher order of stability than the hydrogen bonds discussed above. This process must contribute to some extent to the fall in viscosity, although it would not be expected to be as important as the breakdown of hydrogen bonding in view of the very great decrease brought about by this factor alone during acid treatment (Creeth, Gulland, and Jordan, *loc. cit.*).

The formation of secondary phosphoryl groups when internucleotide linkages are broken is explicable on the basis of a branched or unbranched structure for the polynucleotide chain. However, new primary phosphoryl groups could only be formed as a result of the cleavage of bonds involving tri-esterified phosphoric acid residues. In Part I, the presence of such phosphorus atoms at not infrequent intervals along the main polynucleotide chain was suggested in order to explain the degree of branching implied by the titration data. The formation of primary phosphoryl groups on ultrasonic irradiation therefore supplies additional evidence for this hypothesis. Without further measurements of the size and shape of the fragments produced it is not possible to say whether ultrasonic irradiation breaks the main polynucleotide chain or removes the side branches or has a random effect. Melville and Murray's evidence (*loc. cit.*) that the weaker covalent linkages in synthetic copolymers are not preferentially ruptured by ultrasonic irradiation supports the latter alternative; they found no evidence for the formation of free radicals in their irradiations, which were carried out under conditions where the more effective cavitation could not occur. A free-radical mechanism also seems unlikely in these irradiations of nucleic acid under cavitation conditions, since there is no long-continued steep fall in viscosity after the irradiation has ceased (Laland, Overend, and Stacey, *loc. cit.*; contrast the action of *X*-irradiation in the presence of oxygen, Butler and Conway, *J.*, 1950, 3418).

EXPERIMENTAL.

The sodium salt of herring sperm deoxyribonucleic acid used in these experiments was the sample H_1 of Part I.

The sonic oscillator was that described by Melville and Murray (*loc. cit.*). Aqueous solutions of H_1 (0·2 g./100 ml.) were irradiated at atmospheric pressure for periods of 95, 180, and 270 minutes and were surrounded by a cooling tube which kept the temperature at about 20°. The anode current was kept constant at a value of 70 m. amp. and this ensured that the intensity was the same in all experiments. After irradiation, the viscosity of the solutions was determined (see Table I), and the degraded nucleic acid was isolated by drying in the frozen state.

The nucleic acid solutions were titrated at 25° under a nitrogen atmosphere, and the pH's of the solutions were determined by means of a glass electrode and a saturated calomel half-cell. The concentrations of the solutions used, the method of calibrating the glass electrodes, and the calculations of acid and base combined were the same as those described in Part I. The error in each individual pH measurement was not greater than $\pm$0·01 unit, and the calibration of the electrodes was frequently checked during and after the titrations.

All viscosity measurements were made at 25° in an Ostwald viscometer; η(rel.) in Table I is the ratio of the flow time of 5 ml. of the nucleic acid solution (0·2 g./100 ml.) to the flow time of 5 ml. of distilled water.

The authors are grateful to Professor H. W. Melville, F.R.S., for the use of the sonic oscillator, to Mr. S. Laland for carrying out the irradiations, and to Professor M. Stacey, F.R.S., for his helpful interest in this work. Part of the cost was defrayed by Imperial Chemical Industries Limited, and by the British Empire Cancer Campaign (Birmingham Branch), and one of them (W. A. L.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant.

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[*Received, June 19th*, 1951.]

744. *The Constitution of Products Formed from o-Phenylenediamines and Alloxan in Neutral Solution.*

By F. E. King and J. W. Clark-Lewis.

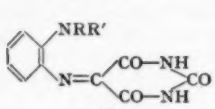
Compounds obtained by the condensation of alloxan with *o*-phenylenediamine and with *N*-methyl- and *N*-phenyl-*o*-phenylenediamine have been shown by methylation studies and the synthesis of degradation products to be quinoxalone-3-carboxyureides and not alloxan-anils (Kühling, *Ber.*, 1893, 26, 540; Kühling and Kaselitz, *ibid.*, 1906, 39, 1314; Rudy and Cramer, *ibid.*, 1938, 71, 1234), thus confirming the structures assigned originally to products of this type by Hinsberg (*ibid.*, 1885, 18, 1228; *Annalen*, 1896, 292, 245).

It is well known from the chemistry of riboflavine that the hydrochlorides of diprimary and primary-secondary *o*-phenylenediamines react with alloxan forming respectively alloxazines (Kühling, *Ber.*, 1891, **24**, 2363) and *iso*alloxazines, *e.g.*, 9-methyl*iso*alloxazine (Kuhn and Weygand, *Ber.*, 1934, **67**, 1409). The condensation of alloxan with the free *o*-diamines, on the other hand, follows a different course and gives products which have generally been formulated as alloxan-anils (I). The first thus represented was obtained from 2-amino-5 : 4′-dimethyldiphenylamine (Kühling, *Ber.*, 1893, **26**, 540), and others prepared from *N*-methyl- and *N*-phenyl-*o*-phenylenediamine and *o*-aminodi-*p*-tolylamine were described by Kühling and Kaselitz (*ibid.*, 1906, **39**, 1314). Later, during the researches on riboflavine, similar compounds were obtained from the condensation of alloxan in various mineral acid-free solvents with 4 : 5-dimethyl-2-methylaminoaniline (Kuhn and Reinemund, *Ber.*, 1934, **67**, 1932), 2-L-arabitylamino-4 : 5-dimethylaniline (Kuhn, Weygand, and Rudy, *ibid.*, 1935, **68**, 633), and 4 : 5-dimethyl-2-D-ribitylaminoaniline (Tishler, Wellman, and Ladenburg, *J. Amer. Chem. Soc.*, 1945, **67**, 2165), and they were likewise designated alloxan-anils. Nevertheless, there is little evidence to support the accepted structures of these products of the acid-free condensation of alloxan and *o*-phenylenediamines. Unlike the authentic Schiff's bases, *e.g.* alloxan-5-*p*-dimethylaminoanil (Piloty and Finckh, *Annalen*, 1904, **333**, 37; see King and Clark-Lewis, *J.*, 1951, 3080), they do not undergo hydrolysis to their original components when treated with mineral acids, nor are they cyclised in acid media to alloxazines or *iso*alloxazines. In contrast, alkaline hydrolysis readily yields derivatives of 3-hydroxyquinoxaline-2-carboxylic acid (III; R = H) or the corresponding keto-compound (II; R = alkyl or aryl), so that Hinsberg (*Ber.*, 1885, **18**, 1228; *Annalen*, 1896, **292**, 245), who in a study of quinoxaline formation first examined the action of *o*-phenylenediamine and of its 4-methyl derivative on alloxan, in fact, formulated these products as 3-hydroxyquinoxaline-2-carboxyureides (IV; R = H). Rudy and Cramer (*Ber.*, 1938, **71**, 1234) sought to differentiate between the alternative structures by comparing the products formed, respectively, from *o*-phenylenediamine or *N*-methyl-*o*-phenylenediamine with that obtained from alloxan and *NN*-dimethyl-*o*-phenylenediamine for which an anil formula (I; R = R′ = Me) alone seemed possible. In view of the observed similarity of all three derivatives, Hinsberg's quinoxaline structure was rejected, each compound being represented as an alloxan-anil. However, it has recently been established (King and Clark-Lewis, *loc. cit.*) that through the participation of one of the *N*-methyl substituents of the tertiary amino-group, the condensation of the primary-tertiary *o*-diamines with alloxan actually affords a spiro-compound (V), thus invalidating the argument used by Rudy and Cramer (*loc. cit.*) and necessitating a re-examination of the problem. A further study of these products, including that derived from *N*-phenyl-*o*-phenylenediamine, has shown that in neutral solution the condensation invariably affords 3-hydroxyquinoxaline-2-carboxyureides or its keto-equivalent (cf. IV or VI) as supposed originally by Hinsberg (*loc. cit.*).

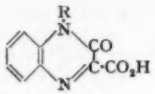
The compound prepared from alloxan and *o*-phenylenediamine in aqueous solution was methylated by diazomethane to a colourless product shown by a Zeisel estimation to be an *O*-methyl derivative. Hydrolysis of this ether with cold aqueous sodium hydroxide resulted in the formation of 3-methoxyquinoxaline-2-carboxylic acid (III; R = Me), identified by comparison with an authentic specimen. The latter was obtained from synthetic 3-hydroxyquinoxaline-2-carboxylic acid by treatment with diazomethane, the resulting methyl 3-methoxyquinoxaline-2-carboxylate then being subjected to gentle hydrolysis. It follows that the original compound is a 3-hydroxyquinoxaline, *i.e.* (IV; R = H), the condensation having been accompanied by fracture of the alloxan ring leaving a carboxyureide residue at position 2. The formation of a

methyl ether, *i.e.* (III; R = Me), from 3-hydroxyquinoxaline-2-carboxylic acid is contrary to the experience of Ohle and Gross (*Ber.*, 1935, **68**, 2262) with ethyl 3-hydroxyquinoxaline-2-carboxylate which when treated with diazomethane yields the *N*-methyl derivative.

From *N*-methyl-*o*-phenylenediamine and alloxan in aqueous solution 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxyureide (VI; R = Me) is obtained, the constitution of the product following from its hydrolysis with boiling 2N-hydrochloric acid to 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid (II; R = Me). This was also synthesised from *N*-methyl-*o*-phenylenediamine and ethyl mesoxalate in the presence of dilute hydrochloric acid (cf. Ohle and Gross, *loc. cit.*), the two specimens being characterised by conversion with diazomethane into the same methyl ester. Methylation of the compounds obtained from both *o*-phenylenediamine and *N*-methyl-*o*-phenylenediamine and alloxan with methyl iodide–potassium carbonate in acetone resulted in the same trimethyl derivative of 3 : 4-dihydro-3-ketoquinoxaline-2-carboxyureide. Obviously one methyl group is attached to the position-4 nitrogen atom, the others being present in the ureido-side-chain, but their precise location has not been ascertained.



(I)



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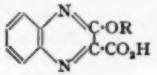
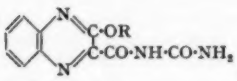
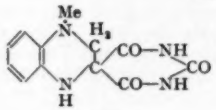


(III)

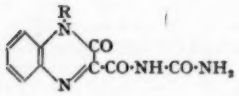
(IV)

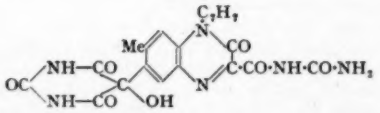




(V)

(VI)





(VII)

Hydrolysis of the trimethyl derivative with aqueous alkali led once more to the formation of 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid.

The condensation of alloxan with *o*-aminodiphenylamine, described by Kühling and Kaselitz (*loc. cit.*), gave an improved yield of product when aqueous ethanol was used as solvent in place of anhydrous alcohol. Its constitution as 3 : 4-dihydro-3-keto-4-phenylquinoxaline-2-carboxyureide (VI; R = Ph) follows from the resemblance of its ultra-violet spectrum to that of the quinoxalones similarly prepared from *o*-phenylenediamine and the corresponding *N*-methyl base, the curves of all three compounds showing the characteristic quinoxaline maxima and minima recorded by Kuhn and Bär (*Ber.*, 1934, **67**, 898). It is less stable than the latter and when it is dissolved in cold N-alkali, some *o*-aminodiphenylamine is slowly deposited, as well as the 3 : 4-dihydro-3-keto-4-phenylquinoxaline-2-carboxylic acid which is precipitated on acidification of the remaining solution. The dihydroketophenylquinoxalinecarboxyureide is, as expected, unaffected by diazomethane, but gives a dimethyl derivative on methylation by the methyl iodide–potassium carbonate method. With hot aqueous alkali this derivative is very largely degraded to *o*-aminodiphenylamine, isolated as the toluene-*p*-sulphonyl derivative.

These observations may be taken generally to exclude the alloxan-anil formulation in favour of the quinoxalone structure. For example, the compound formed in neutral solution from 5 : 6-diaminoquinoline and alloxan, and represented as an alloxan Schiff's base (Rudy, *Ber.*, 1938, **71**, 847), is doubtless 2-hydroxypyridino(3′ : 2′-5 : 6)quinoxaline-2-carboxyureide or the isomeric pyridino(3′ : 2′-7 : 8)quinoxaline. From the 2-alkylamino-3-aminopyridines, however, Rudy and Majer (*ibid.*, p. 1323) have obtained two series of products, one yellow and unstable, which the authors represent as alloxan-anils, and the other colourless and formed by the ready isomerisation of the former, to which they have assigned the keto-triazanaphthalenecarboxyureide structure. As the dihydroketoquinoxaline-carboxylic acids and -carboxyureides are invariably yellow further data are necessary to determine the precise constitution of these derivatives of 2 : 3-diaminopyridine.

The revision of structure clarifies several previously anomalous features in the chemistry of these products of the neutral condensation of alloxan with *o*-diamines. It is obvious, for

example, why they do not show the properties of a free 2-amino-group expected from their representation as alloxan-anils, and their failure to yield alloxazines (or *iso*alloxazines) when treated with acid is seen to be a natural consequence of the inability of all but the most drastic reagents to effect a ring-closure requiring the interaction of two amido-groups. A compound obtained from alloxan and 2-amino-5 : 4′-dimethyldiphenylamine in hot ethanolic hydrochloric acid, and shown by Kühling (*loc. cit.*) to contain two alloxanyl residues (see also Rudy, *Oest. Chem.-Zeit.*, 1939, **42**, 329), is almost certainly the quinoxalyldialuric acid (VII).

Experimental.

3-*Hydroxyquinoxaline-2-carboxyureide* (IV; R = H).—The quinoxalinecarboxyureide was obtained in 90% yield by mixing cold aqueous solutions of equimolecular quantities of alloxan hydrate and *o*-phenylenediamine (Hinsberg, *Ann.*, 1896, **292**, 245). Recrystallisation from acetic acid gave yellow needles, m. p. 250° (decomp.) (Found : C, 52·1; H, 3·8; N, 24·3. Calc. for $C_{10}H_8O_3N_4$: C, 51·7; H, 3·5; N, 24·1%). Ultra-violet light absorption in 95% ethanol : maxima at 234 mμ (ε = 22,900), 312 mμ (ε = 9300), and 393 mμ (ε = 5840); and minima at 218 mμ (ε = 17,500), 270 mμ (ε = 3530), and 350 mμ (ε = 3670).

3-*Methoxyquinoxaline-2-carboxyureide* (IV; R = Me).—The ureide (IV; R = H) (3 g.) was treated with excess of ethereal diazomethane, and the suspension filtered after 96 hours. Evaporation of the filtrate gave 3-*methoxyquinoxaline-2-carboxyureide*, colourless needles (0·3 g.) (from methanol), m. p. 225°, a further quantity (0·9 g.) of somewhat impure material being obtained from the ether-insoluble residue (Found : C, 54·1; H, 3·9; N, 22·7; OMe, 12·2. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1; N, 22·8; OMe, 12·6%).

3-*Methoxyquinoxaline-2-carboxylic Acid* (III; R = Me).—(*a*) 3-Methoxyquinoxaline-2-carboxyureide (0·22 g.) dissolved rapidly in cold aqueous sodium hydroxide (10 c.c.; N); after 72 hours at room temperature the solution was acidified with hydrochloric acid (10N), and the precipitated acid (0·143 g., 84%), m. p. 130° (decomp.), collected and recrystallised from hot water (14 c.c.). 3-*Methoxyquinoxaline-2-carboxylic acid* was obtained in colourless needles, m. p. 132° (decomp.) (Found : N, 14·3; OMe, 14·8. $C_{10}H_8O_3N_2$ requires N, 13·7; OMe, 15·2%).

(*b*) 3-Hydroxyquinoxaline-2-carboxylic acid (III; R = H), prepared from *o*-phenylenediamine and ethyl mesoxalate in dilute hydrochloric acid solution (Ohle and Gross, *loc. cit.*; Gowenlock, Newbold, and Spring, *J.*, 1945, 622), dissolved rapidly in ethereal diazomethane; after removal of the ether the residue was crystallised from methanol, yielding *methyl* 3-*methoxyquinoxaline-2-carboxylate* as colourless needles, m. p. 107° alone or mixed with the methyl ester of the acid derived from (IV; R = Me) (Found : C, 60·6; H, 4·6; N, 12·4. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%). The methyl ester (0·2 g.) dissolved readily in aqueous sodium hydroxide (12 c.c.; N), and when the solution was acidified with 2N-hydrochloric acid, and the precipitated solid crystallised from hot water, 3-methoxyquinoxaline-2-carboxylic acid (0·15 g., 80%) was obtained; it had m. p. 132° (decomp.), not depressed by the acid obtained from (IV; R = Me).

3-Hydroxyquinoxaline-2-carboxyureide is not only easily hydrolysed by cold 2N-sodium hydroxide, but 3-hydroxyquinoxaline-2-carboxylic acid (0·5 g., 61%), m. p. 268° (decomp.), was obtained when the ureide (1 g.) was boiled with 2N-hydrochloric acid (50 c.c.); the dimethyl derivative obtained with diazomethane had m. p. and mixed m. p. 107°.

3 : 4-*Dihydro-3-keto-4-methylquinoxaline-2-carboxyureide* (VI; R = Me).—A solution of alloxan hydrate (11 g.) in water (50 c.c.) was added to *N*-methyl-*o*-phenylenediamine (7 g.) in ethanol (100 c.c.). Precipitation of a yellow solid (13·4 g., 78%), m. p. 248° (decomp.), began instantly and this was collected after 1 hour. Recrystallisation of the product from acetic acid gave 3 : 4-*dihydro-3-keto-4-methylquinoxaline-2-carboxyureide* (VI; R = Me) in yellow plates, m. p. 247° (decomp.) (Kühling and Kaselitz, *loc. cit.*, give m. p. 224°, and Rudy and Cramer, *loc cit.*, m. p. 250°) (Found : C, 54·1; H, 4·1; N, 23·6. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1; N, 22·8%). Ultra-violet light absorption in 95% ethanol : maxima at 236 mμ (ε = 26,100), 317 mμ (ε = 9000), and 387 mμ (ε = 5880); and minima at 219 mμ (ε = 16,900), 268 mμ (ε = 3240), and 348 mμ (ε = 4170).

Methyl 3 : 4-*Dihydro-3-keto-4-methylquinoxaline-2-carboxylate*.—(*a*) The ureide (VI; R = Me) (1 g.) was boiled with 2N-hydrochloric acid (50 c.c.) until dissolution was complete (*ca.* 15 minutes) and thereafter for 10 minutes. 3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid (II; R = Me) (0·75 g., 90%) crystallised from the cold solution in yellow needles, m. p. 166° raised to 173—174° (decomp.) by recrystallisation from water. Methylation of the acid with ethereal diazomethane gave *methyl* 3 : 4-*dihydro-3-keto-4-methylquinoxaline-2-carboxylate*, which separated from methanol in pale yellow needles, m. p. 126° (Found : C, 60·0; H, 4·4; N, 12·9. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%).

(*b*) 3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid m. p. 173—174° (decomp.), was prepared from *N*-methyl-*o*-phenylenediamine and ethyl mesoxalate in N-hydrochloric acid (cf. Ohle and Gross, *loc. cit.*). With diazomethane this yielded the methyl ester as pale yellow needles, m. p. 126° alone or mixed with the product derived from (VI; R = Me).

3 : 4-*Dihydro-3-keto-4-methylquinoxaline-2-carboxydimethylureide*.—(*a*) 3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxyureide (2 g.), anhydrous potassium carbonate (10 g.), methyl iodide (10 g.), and acetone (30 c.c.) were heated under reflux for 24 hours. The mixture was then shaken with water, and the solution extracted with chloroform; the extract when washed, dried, and evaporated yielded an oil which solidified to hard yellow prisms (2·15 g.), m. p. 192°. Recrystallisation from ethanol (50 c.c.) gave 3 : 4-*dihydro-3-keto-4-methylquinoxaline-2-carboxydimethylureide* (1·25 g.), as colourless prisms,

m. p. 194° (Found: C, 57·4; H, 5·3; N, 20·1; OMe, 0; NMe, 23·9. $C_{13}H_{14}O_3N_4$ requires C, 56·9; H, 5·2; N, 20·4; NMe, 31·8%. *M*, determined by Dr. S. C. Wallwork from *X*-ray diffraction, 275; theory, 274). Light absorption in 95% ethanol: maxima at 225 mμ (ε = 30,400) and 302 mμ (ε = 4350); and minimum at 278 mμ (ε = 1950).

(*b*) The methylation of 3-hydroxyquinoxaline-2-carboxyureide (3 g.) with methyl iodide–potassium carbonate for 14 hours gave colourless prisms (1·9 g., 54%), m. p. 194°, identical with the product described above. The methylated ureide was hydrolysed with boiling 2N-sodium hydroxide and, after the solution had been cleared with chloroform, it was acidified and the product extracted with chloroform. The residue left on evaporation of the solvent was crystallised from hot water, which gave 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid (30%), m. p. 173—174° (decomp.) alone or mixed with an authentic specimen, the methyl ester having m. p. and mixed m. p. 126°.

3 : 4-*Dihydro*-3-*keto*-4-*phenylquinoxaline*-2-*carboxyureide* (VI; R = Ph).—*N*-Phenyl-*o*-phenylenediamine, prepared by shaking *o*-nitrodiphenylamine for 3 hours in hydrogen at 75 lbs./sq. in. over Raney nickel (yield 90%) (cf. Elderfield and McCarthy, *J. Amer. Chem. Soc.*, 1951, **73**, 975), was characterised as 2-(*toluene*-p-*sulphonamido*)*diphenylamine* which crystallised from aqueous ethanol in needles, m. p. 132° (Found: C, 67·7; H, 5·0. $C_{19}H_{18}O_2N_2S$ requires C, 67·4; H, 5·3%). The toluene-*p*-sulphonyl derivative is soluble in aqueous sodium hydroxide and gives a blue-violet colour with nitric acid. 3 : 4-*Dihydro*-3-*keto*-4-*phenylquinoxaline*-2-*carboxyureide* was obtained in 50% yield from the amine and alloxan in aqueous ethanol (cf. Kühling and Kaslitz, *loc. cit.*). The reaction is much faster in aqueous ethanol (*ca.* ½ hour), and the product is not contaminated with the dark green impurity otherwise formed. Crystallisation from aqueous acetic acid gave the ureide (VI; R = Ph) in yellow prisms, m. p. 244° (Found: C, 62·8; H, 3·6; N, 18·2. $C_{16}H_{12}O_3N_4$ requires C, 62·3; H, 3·9; N, 18·2%). Light absorption in 95% ethanol: maxima at 230 mμ (ε = 20,100), 310 mμ (ε = 6600), and 378 mμ (ε = 3960); and minima at 220 mμ (ε = 18,800), 268 mμ (ε = 3680), and 350 mμ (ε = 3450).

A solution of the ureide (0·5 g.) in aqueous sodium hydroxide (25 c.c.; N) was filtered after 3 days from red needles of *N*-phenyl-*o*-phenylenediamine (0·081 g., 27%); acidification of the filtrate gave 3 : 4-dihydro-3-keto-4-phenylquinoxaline-2-carboxylic acid (0·185 g., 43%), m. p. of the unpurified acid 158—160° (decomp.) (cf. Kühling and Kaselitz, *loc. cit.*).

3 : 4-*Dihydro*-3-*keto*-4-*phenylquinoxaline*-2-*carboxydimethylureide*.—The ureide (VI; R = Ph) (8 g.), anhydrous potassium carbonate (24 g.), methyl iodide (24 g.), and acetone (70 c.c.) were refluxed for 18 hours. After addition of water, the product was isolated with chloroform, and when crystallised gave 3 : 4-*dihydro*-3-*keto*-4-*phenylquinoxaline*-2-*carboxydimethylureide* (7·7 g., 88%) as colourless prisms, m. p. 209° (Found: C, 64·0; H, 4·7; N, 16·8; NMe, 12·1. $C_{18}H_{16}O_3N_4$ requires C, 64·1; H, 5·1; N, 16·8; NMe, 17·3%). Light absorption in 95% ethanol: maximum at 301 mμ (ε = 3525); minimum at 279 mμ (ε = 1800).

This carboxydimethylureide (3·4 g.) was heated with ethanol (60 c.c.) and aqueous sodium hydroxide (60 c.c.; 2N) for 3 hours, and the alcohol removed by evaporation on a steam-bath. Extraction of the aqueous solution with ether gave *N*-phenyl-*o*-phenylenediamine (1·4 g., 75%). The base (1·1 g.) was heated on a steam-bath for ½ hour with toluene-*p*-sulphonyl chloride (1·2 g.) and pyridine (5 ml.), and the mixture poured into ice–water. Crystallisation of the precipitate from aqueous ethanol (charcoal) gave 2-(toluene-p-sulphonamido)diphenylamine (0·8 g.) in needles, m. p. 132° alone or mixed with the authentic specimen already described.

THE UNIVERSITY, NOTTINGHAM. [*Received, August 3rd*, 1951.]

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745. *The Caryophyllenes. Part IX.* Homocaryophyllenic Acid.*

By T. L. DAWSON and G. R. RAMAGE.

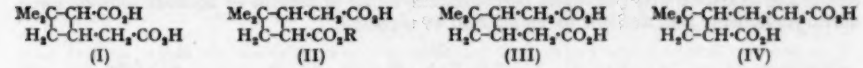
2-Carboxymethyl-3 : 3-dimethyl*cyclo*butylacetic acid (3 : 3-dimethyl*cyclo*butane-1 : 2-diacetic acid) (III) and β-(4-carboxy-2 : 2-dimethyl*cyclo*butyl)-propionic acid (IV) have been prepared, and the latter is shown to be identical with homocaryophyllenic acid by reference to the corresponding amides, anilides, and *p*-toluidides. A proposed synthesis of caryophyllenic acid (II; R = H) has been prevented by an anionotropic change; a new route to norcaryophyllenic acid is described.

DAWSON and RAMAGE (*J.*, 1950, 3523) showed that 2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid (I) was not identical with caryophyllenic acid, which was therefore (II) by exclusion. Campbell and Rydon (*Chem. and Ind.*, 1951, 312) have since reported the synthesis of the racemic form of (II) which is considered to be identical with caryophyllenic acid on the evidence of infra-red spectra.

The next step in establishing the structure of caryophyllene necessitates consideration of homocaryophyllenic acid, which is available by the sodium hypobromite oxidation of a $C_{11}H_{18}O_3$ keto-acid, one of the principal and most characteristic degradation products. Homo-

* Part VIII, *J.*, 1950, 3523.

caryophyllenic acid has now been isolated from the acids obtained by oxidation of γ-caryophyllene. Homocaryophyllenic acid must be represented by either (III) or (IV) although earlier work by Ramage and Simonsen (*J.*, 1937, 73) had failed to relate it to products derived from



(I) (II) (III) (IV)

norcaryophyllenic or caryophyllenic acid. The substance (III) was then prepared from norcaryophyllenic acid and characterised by *cis*- and *trans*-dianilides, m. p. 170° and m. p. 280°. These were taken to correspond to the *cis*- and *trans*-dianilides, m. p. 180° and m. p. 282°, obtained from homocaryophyllenic acid and, though they were shown to be different by *X*-ray powder photographs, this was attributed to complication by the possibility of racemisation.

A re-examination of the synthesis of (III) from norcaryophyllenic acid has been possible by using the more convenient Arndt–Eistert reaction, and the resulting dianilides, now optically active, had m. p. 170° and m. p. 282—283°. It was found that the new anilide of m. p. 170° was dextrorotatory, whilst *cis*-homocaryophyllenic acid dianilide, m. p. 180°, was lævorotatory. The dianilides of m. p. 282° gave no depression of the melting point on admixture, but this is not proof of identity since the *trans*-dianilides of norcaryophyllenic and caryophyllenic acid also have the same melting point and give no depression on admixture. The dianilides thus appeared to be unsatisfactory as a means of identification, and the *p*-toluidides have been prepared. Only the *trans*-di-*p*-toluidides were obtained crystalline, and products from substance (III) and homocaryophyllenic acid had m. p. 182° and 227° respectively. On this basis homocaryophyllenic acid must be represented by (IV) and this is confirmed by a new route to this structure which utilises the half ester of caryophyllenic acid previously described by Ruzicka, Bardhan, and Wind (*Helv. Chim. Acta*, 1931, **14**, 423). Mild hydrolysis of methyl caryophyllenate will almost certainly give (II; R = Me); after conversion of this into the corresponding acid chloride and application of the Arndt–Eistert reaction, the resulting ester corresponding to (IV) was shown to be identical with ethyl homocaryophyllenate by the derived *cis*- and *trans*-dianilides and the *trans*-di-*p*-toluidide. Preliminary treatment of the acid with concentrated hydrochloric acid in a sealed tube at 150° increased the proportion of the *trans*-forms of the dianilide and the di-*p*-toluidide, m. p. 282—283° and 227° respectively, thus providing evidence for the configurations of these compounds.

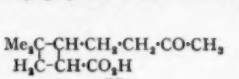
A previous preparation which should have given the dimethyl ester of (IV) (Ramage and Simonsen, *loc. cit.*) led to a dianilide of m. p. 206° and is considered to have involved racemisation of one asymmetric centre; this would undoubtedly occur in the formation of caryophyllenic anhydride by treatment with acetic anhydride at 220°, since complete racemisation occurs under these conditions in the formation of norcaryophyllenic acid anhydride (on hydrolysis this gives inactive norcaryophyllenic acid).

Although the issue is complicated by *cis-trans*- and optical isomerism, it is considered to be established that homocaryophyllenic acid is correctly represented by (IV) and its relation to the $C_{11}H_{18}O_3$ keto-acid has been further examined. The keto-acid is very readily oxidised by potassium permanganate at 50° to yield, by loss of two carbon atoms, a mixture of *cis*- and *trans*-forms of caryophyllenic acid. This, taken in conjunction with the structure (IV) for homocaryophyllenic acid, necessitates structure (V) for the keto-acid.

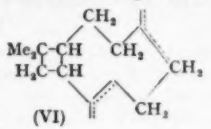
The present work, coupled with previous degradative experiments on caryophyllene, justifies the caryophyllene formula based on (VI) reported by Dawson, Ramage, and Wilson (*Chem. and Ind.*, 1951, 464). A nine-membered ring formula (VII) for caryophyllene was first suggested by Sörm, Dolejš, and Plíva (*Coll. Czech. Chem. Comm.*, 1950, **15**, 186) and this view was subsequently confirmed by Barton and Lindsey (*Chem. and Ind.*, 1951, 313) who provided evidence of the grouping $-C(:CH_2)\cdot CH_2\cdot CH_2\cdot CH:CMe-$. Barton (*J. Org. Chem.*, 1950, **15**, 457) favoured (IV) for homocaryophyllenic acid without advancing additional experimental evidence but the above publication with Lindsey appears to indicate acceptance of (III) and not (IV).

Further experiments have been possible on 7 : 7-dimethyl*bicyclo*[3 : 2 : 0]hept-2-ene (VIII; X = H) (Dawson and Ramage, *loc. cit.*). On treatment with *N*-bromosuccinimide the hydrocarbon was smoothly converted into a bromo-derivative (VIII; X = Br) which, with dimethylamine, gave a basic product subsequently shown to have structure (IX; X = NMe_2) and not (VIII; X = NMe_2). This was proved by reduction of the basic product to the saturated amine, which after Hofmann degradation and oxidation gave (I) and not (II). It appears that the rearrangement making this result possible must have occurred during the treatment of (VIII; X = Br) with dimethylamine. Similar rearrangements have been observed on treatment of

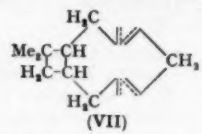
allylic bromides with amines (Jones, Lacey, and Smith, *J.*, 1946, 940) and this provides a further example of three-carbon anionotropy (Braude, *Quart. Reviews*, 1950, **4**, 404). Attempts to convert (IX; X = NMe_3) into (IX; X = H) by Emde reduction have not yet been successful and oxidation with potassium permanganate either in acetone or aqueous solution gave norcaryophyllenic acid and not an amino-acid as expected.



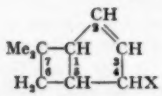
(V)



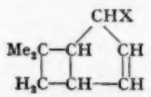
(VI)



(VII)



(VIII)



(IX)

A new synthesis of norcaryophyllenic acid has been accomplished from the bromo-compound (VIII; X = Br). Treatment with silver oxide produced an unstable unsaturated alcohol, which, the rearrangement being assumed, would have structure (IX; X = OH). Oxidation gave (±)-norcaryophyllenic acid, and the *cis*-form was identical with the product prepared by Ruzicka and Zimmermann (*Helv. Chim. Acta*, 1935, **18**, 219) by a method involving conversion of an active *trans*-acid by acetic anhydride into the (±)-*cis*-anhydride.

Experimental.

(Analyses by Drs. Weiler and Strauss, Oxford.)

The dianilides and di-*p*-toluidides described in this paper were prepared by Hardy's method (*J.*, 1936, 398) from the appropriate ester and Grignard reagent, though better yields were obtained by way of the acid chlorides.

Oxidation of γ-Caryophyllene.—The γ-caryophyllene used for the oxidation was obtained from the mother-liquors remaining after the preparation of β-caryophyllene nitrosite (Deussen and Lewinsohn, *Annalen*, 1907, **356**, 13) and had b. p. 120°/12 mm., n_D^{19} 1·4965, d_{18}^{18} 0·8964, and $[\alpha]_D^{19}$ −23·95°. Oxidation with nitric acid (Ramage and Simonsen, *loc. cit.*) gave a mixture of acids, the esters from which on one fractionation through a Towers unit (see Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green & Co., 1948, p. 100) gave: (i) dimethyl *as*-dimethylsuccinate (47·0 g.), b. p. 82—85°/12 mm., n_D^{18} 1·4238; (ii) dimethyl norcaryophyllenate (14·5 g.), b. p. 110—114°/15 mm., n_D^{18} 1·4410; (iii) dimethyl caryophyllenate (25·0 g.), b. p. 129—133°/15 mm., n_D^{18} 1·4452; and (iv) dimethyl homocaryophyllenate (10·2 g.), b. p. 141—145°/15 mm., n_D^{18} 1·4489. The acids from fractions (iii) and (iv) were used below without preliminary separation of the *cis*- and *trans*-forms. Fraction (iv) was identified by preparation of the *cis*- and *trans*-dianilides, m. p. 180° and 282—283° respectively, alone or admixed with the corresponding dianilides of authentic homocaryophyllenic acid.

2-Carboxymethyl-3 : 3-dimethylcyclobutylacetic (3 : 3-Dimethylcyclobutane-1 : 2-diacetic) Acid (III).—Norcaryophyllenic acid (17·4 g.) was set aside with thionyl chloride (30 c.c.) at room temperature for 4 hours before the excess of thionyl chloride was removed under reduced pressure. Fractionation of the product gave norcaryophyllenoyl dichloride (15·1 g.), b. p. 103—105°/12 mm. This acid chloride (5·6 g.), dissolved in dry ether, was added in small portions to an ethereal solution of diazomethane (containing *ca.* 6 g. of diazomethane) at 0—5°, and the mixture allowed to attain room temperature overnight. The ether and excess of diazomethane were removed under reduced pressure at room temperature, giving the bisdiazoketone (6·0 g.) as a viscous gum. This was dissolved in methyl alcohol (75 c.c.) and kept at 50—60° whilst silver oxide (2·0 g.) was added in small portions during 2 hours, by which time the evolution of nitrogen had almost ceased. The reaction was completed on the water-bath (15 minutes). The cooled mixture was filtered, the filtrate was evaporated, and the residue on fractionation gave methyl 2-carbomethoxymethyl-3 : 3-dimethylcyclobutylacetate (4·2 g.), b. p. 140—144°/12 mm., n_D^{18} 1·4520, d_{18}^{18} 1·052, $[\alpha]_D^{17}$ +21·3°. The trans-*dianilide*, which was insoluble in ether, crystallised from cyclohexanone in small needles, m. p. 282—283° (Found: C, 75·1; H, 7·2. $C_{22}H_{24}O_2N_2$ requires C, 75·4; H, 7·5%). The cis-*dianilide*, which was soluble in ether, crystallised from aqueous ethyl alcohol (60%) in shining plates, m. p. 170°, $[\alpha]_D^{18}$ +42·9° (*c*, 1·706 in chloroform) (Found: C, 75·0; H, 7·2%). The *diamide*, prepared by keeping the above ester in ammonia solution (*d* 0·880) in a sealed tube for several weeks, crystallised from dioxan in small needles, m. p. 154° (Found: C, 60·1; H, 9·2. $C_{10}H_{16}O_2N_2$ requires C, 60·6; H, 9·1%). The trans-*di*-p-*toluidide*, which was sparingly soluble in ether, crystallised from ethyl alcohol in flat needles, m. p. 182°, $[\alpha]_D^{20}$ +68·7° (*c*, 0·5825 in acetone) (Found: C, 76·0; H, 8·0. $C_{24}H_{32}O_2N_2$ requires C, 76·2; H, 8·0%). Homocaryophyllenic acid prepared from the $C_{11}H_{18}O_3$ keto-acid (Ramage and Simonsen, *J.*, 1937, 73) gave a trans-*di*-p-*toluidide*, m. p. 227° (Found: C, 76·2; H, 7·9%), but the diamide prepared as above could only be obtained as an oil.

The above rearrangement of the bisdiazoketone was also carried out in aqueous solution to give the acid which was converted into the ester, but the yields were considerably lower.

β-(2-Carboxy-4 : 4-dimethylcyclobutyl)propionic Acid (IV).—On treatment with thionyl chloride, the half ester (5·4 g.) of caryophyllenic acid gave the ester-chloride (4·0 g.), b. p. 125—128°/14 mm.,

which in dry ether was added to ethereal diazomethane (*ca.* 2·5 g. of diazomethane) at 0—5° and the mixture allowed to attain room temperature overnight. Removal of the ether and diazomethane under reduced pressure gave the diazoketone (4·3 g.). This was dissolved in dry methyl alcohol (45 c.c.) and kept at 50—60° while silver oxide (2·0 g.) was added in portions during 2 hours. The reaction was completed by refluxing the mixture for ½ hour. The cooled mixture was filtered, the filtrate was evaporated, and the residue on fractionation gave methyl β-(2-carbomethoxy-4 : 4-dimethyl*cyclo*butyl)propionate (2·85 g.), b. p. 140—145°/12 mm., n_D^{19} 1·4498, d_{19}^{19} 1·047, $[\alpha]_D^{20}$ +30·1°. The derived *trans*-dianilide, which was insoluble in ether, crystallised from *cyclo*hexanone in small needles, m. p. 282—283° (Found : C, 75·4; H, 7·4. Calc. for $C_{23}H_{26}O_2N_2$: C, 75·4; H, 7·5%). The *cis*-dianilide, which was soluble in ether, crystallised from aqueous ethyl alcohol (60%) in shining plates, m. p. 180° (alone and admixed with *cis*-homocaryophyllenic dianilide), $[\alpha]_D^{19}$ −34·6° (*c*, 1·737 in chloroform) (Found : C, 75·0; H, 7·2%). The *trans*-di-*p*-toluidide crystallised from ethyl alcohol in balls of needles, m. p. 227° (alone and admixed with homocaryophyllenic di-*p*-toluidide) (Found : C, 76·2; H, 7·9. Calc. for $C_{24}H_{30}O_2N_2$: C, 76·2; H, 8·0%).

Oxidation of the $C_{11}H_{18}O_3$ *Keto-acid* (V).—The keto-acid (2·0 g.) was dissolved in sodium carbonate solution (2N. ; 30 c.c.) and oxidised by the addition of aqueous potassium permanganate (3% ; 195 c.c.) to the solution at 50° during 5 hours. Acidification of the filtered solution followed by ether-extraction gave an acid (1·6 g.) which was esterified with ethereal diazomethane. Distillation afforded dimethyl caryophyllenate (1·3 g.), b. p. 128—133°/17 mm., n_D^{17} 1·4461. The ester was hydrolysed with potassium hydroxide (1·0 g.) and methyl alcohol (10 c.c.), and the sparingly soluble potassium salt which separated was filtered off from the ice-cold solution. Acidification and extraction of the salt gave (+)-*trans*-caryophyllenic acid (0·6 g.) which crystallised from *cyclo*hexane in long needles, m. p. 80—81° [alone or admixed with authentic (+)-*trans*-caryophyllenic acid]. From the potassium salt filtrate was obtained a liquid acid which after treatment with acetic anhydride in a sealed tube at 220° and hydrolysis of the anhydride formed gave *cis*-caryophyllenic acid (0·3 g.), m. p. 77—78° (alone or in admixture)

7 : 7-*Dimethyl*-2-*dimethylamino*bicyclo[3 : 2 : 0]*hept*-3-*ene* (IX; X = NMe_2).—The hydrocarbon (VIII) (4·5 g.) in carbon tetrachloride (30 c.c.) was refluxed for 5 minutes with *N*-bromosuccinimide (6·5 g.). The filtrate was poured into dimethylamine in carbon tetrachloride (13% w/v; 28 c.c.) and refluxed for ½ hour. Dimethylamine hydrobromide was filtered off and the solvent removed under reduced pressure. The residue was treated with ether, and the base extracted with dilute sulphuric acid. The acid extract was made alkaline with sodium hydroxide solution and extracted with ether. Removal of the solvent from the dried extract and fractionation gave 7 : 7-*dimethyl*-2-*dimethylamino*bicyclo[3 : 2 : 0]*hept*-3-*ene* (3·7 g.), b. p. 80—81°/17 mm., n_D^{20} 1·4568, d_{21}^{21} 0·8846 (Found : C, 79·9; H, 11·9. $C_{11}H_{19}N$ requires C, 79·9; H, 11·6%). The amine *picrate* crystallised from ethyl alcohol in balls of flat yellow needles, m. p. 177° (Found : C, 51·3; H, 5·5. $C_{17}H_{22}O_7N_4$ requires C, 51·8; H, 5·6%).

7 : 7-*Dimethyl*-2-*dimethylamino*bicyclo[3 : 2 : 0]*heptane*.—The above amine (7·3 g.) was hydrogenated at atmospheric pressure in methyl alcohol using palladium–charcoal (2 g.) as catalyst. Intake of hydrogen was 1104 c.c. (theoretical intake at room pressure and temperature = 1090 c.c.). The solution was filtered, the methyl alcohol was removed, and the residue on fractionation gave 7 : 7-*dimethyl*-2-*dimethylamino*bicyclo[3 : 2 : 0]*heptane* (6·6 g.), b. p. 79—80°/14 mm., n_D^{20} 1·4638 (Found : C, 78·3; H, 12·6. $C_{11}H_{21}N$ requires C, 79·0; H, 12·7%). The saturated amine *picrate* crystallised from ethyl alcohol in clusters of yellow prisms, m. p. 161° (Found : C, 51·6; H, 5·8. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1%).

Hofmann Degradation of the Saturated Amine.—The above saturated amine (3·6 g.) in ethyl acetate was treated with a slight excess of methyl iodide, the solution warmed for 5 minutes after the initial spontaneous reaction, and the methiodide which separated filtered off. The methiodide, m. p. 258° (decomp.), was dissolved in methyl alcohol and shaken for ½ hour with excess of moist silver oxide, and the solution filtered. The methyl alcohol was removed from the filtrate, and the residue heated in an oil-bath until nothing further distilled. The oily distillate was shaken with dilute sulphuric acid and the oil collected in a little ether. Removal of the ether from the dried extract and fractionation gave 7 : 7-dimethyl*bicyclo*[3 : 2 : 0]hept-2-ene (1·5 g.), b. p. 131—134°, n_D^{20} 1·4570. The sulphuric acid extract was made alkaline and the original saturated amine (0·5 g.) recovered.

Oxidation of the Hydrocarbon from the Above Reaction.—The above hydrocarbon (1·8 g.) was oxidised with potassium permanganate (7·0 g.) in acetone (50 c.c.) at 0°. The acid isolated from the sludge did not give a sparingly soluble potassium salt with alcoholic potassium hydroxide and on storage solidified completely. Crystallisation from *cyclo*hexane gave (±)-*cis*-2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid, in prisms, m. p. 120—121° alone or mixed with the *cis*-acid obtained from (IX; X = H).

3 : 3-*Dimethyl*cyclo*butane*-1 : 2-*dicarboxylic Acid*.—*N*-Bromosuccinimide (5·4 g.) was added to the hydrocarbon (VIII; X = H) (3·7 g.) in carbon tetrachloride (15 c.c.), and the mixture warmed on the water-bath for 5 minutes. The precipitated succinimide was filtered off from the cooled solution, and the filtrate shaken with moist silver oxide (8·0 g.) for 1 hour. The silver oxide and bromide were filtered off and the dried solution on evaporation under reduced pressure gave the unsaturated alcohol, which, like the bromo-compound, decomposed on distillation, and without further purification was dissolved in acetone and oxidised by the slow addition of potassium permanganate (11·6 g.) to the solution at 0°. The sludge was filtered off, suspended in water, and decolorised with sulphur dioxide. The acidified solution was extracted with ether, and the acid component isolated with sodium carbonate solution. The alkaline extract was further oxidised by the addition of aqueous potassium permanganate solution (3%) until the colour was permanent. The filtered and acidified solution was extracted with ether. Removal of the solvent from the dried extract gave an acid (1·4 g.). Crystallisation from *cyclo*hexane afforded a crude acid, m. p. 146—148°, which was heated with acetic anhydride in a sealed tube at 220° for 6 hours. Distillation gave the anhydride which on digestion with water and evaporation gave pure

(±)-*cis*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid, which crystallised from benzene in prisms, m. p. 149—150° [alone or admixed with (±)-*cis*-norcaryophyllenic acid described below] (Found: C, 56·1; H, 6·8. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%). The *cis*-dianilide, which was insoluble in ether, crystallised from ethyl alcohol in balls of needles, m. p. 267° (alone or admixed with *cis*-norcaryophyllenic dianilide) (Found: C, 74·2; H, 6·7. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·9%). The *cis*-acid was heated with concentrated hydrochloric acid in a sealed tube at 180° overnight, and the solution was treated with charcoal and evaporated. Crystallisation of the residual acid from *cyclo*hexane gave (±)-*trans*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid in prisms, m. p. 148—149° [alone or admixed with (±)-*trans*-norcaryophyllenic acid described below] (Found: C, 55·6; H, 7·1. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%). The trans-*dianilide*, which was soluble in ether, crystallised from aqueous ethyl alcohol (60%) in flat needles, m. p. 238° (alone or admixed with *trans*-norcaryophyllenic dianilide) (Found: N, 8·8. $C_{20}H_{22}O_2N_2$ requires N, 8·7%).

Racemisation of (+)-trans-*Norcaryophyllenic Acid.*—(+)-*trans*-Norcaryophyllenic acid (0·65 g.) was heated with acetic anhydride (6 c.c.) in a sealed tube at 220° for 6 hours. Distillation of the product afforded an anhydride (0·4 g.) which on digestion with water and evaporation gave (±)-*cis*-norcaryophyllenic acid, which crystallised from benzene in prisms, m. p. 149—150°. The (±)-*cis*-acid was heated with concentrated hydrochloric acid in a sealed tube at 150° for 15 hours. The solution, after treatment with charcoal, was evaporated and gave (±)-*trans*-norcaryophyllenic acid, which crystallised from *cyclo*hexane in prisms, m. p. 148—149°. The (±)-*trans*-dianilide crystallised from aqueous ethyl alcohol (60%) in flat needles, m. p. 238°, and the (±)-*cis*-dianilide crystallised from ethyl alcohol in balls of needles, m. p. 267°.

The authors thank Imperial Chemical Industries Limited for chemicals, the Chemical Society for a research grant, and the Huddersfield Education Authority for the Joseph Blamires Scholarship awarded to one of them (T. L. D.).

THE TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, July 13th*, 1951.]

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746. *Polyene Acids. Part II.* The Stereochemistry of the β-Methylmuconic Acids.*

By J. A. ELVIDGE, R. P. LINSTEAD, and PETER SIMS.

The preparation, by Pauly *et al.*, of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (I) from 3-nitro-*p*-cresol and sulphuric acid, and the isomerisation of the derived lactonic ester (II) with sodium alkoxide to a β-methylmuconic half-ester (III) have been re-investigated. The lactonisation of the half-ester (III) and the derived β-methylmuconic acid (IV) to reafford (II) and (I) have been effected. The half-amide (XIII), prepared from (III) and ammonia, also cyclises readily to the lactonic amide (XIV). Partial hydrolysis of methyl β-methylmuconate (V) gives a second half-ester (VIII) which could not be lactonised; nor could the second acid amide (XII). The compounds (I) and (IV) have also been prepared direct by oxidation of *p*-cresol and of homocatechol with peracetic acid. Conversion of (IV) into a high-melting β-methylmuconic acid, also prepared from β-methyladipic acid, occurs with hot alkali.

The evidence bearing on the configuration of these substances is reviewed. It is concluded that the high-melting acid is *trans-trans*, and that Pauly's acid (IV) is *cis-trans*, contrary to Rinkes.

In the course of the work the three positional isomers of dihydro-β-methylmuconic acid were obtained (Δ^{α}, Δ^{β}, Δ^{γ}), and also the two saturated lactonic acids (XV) and (XVIII).

β-METHYLMUCONIC acid is of especial interest as a dicarboxyisoprene. Its stereoisomerism has a significant connection with that of the carotenoids. We have now investigated this compound and the derived unsaturated lactonic acid, by using essentially the methods by which the parent muconic acids were examined (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228; Elvidge, Linstead, Sims, and Orkin, *ibid.*, p. 2235).

The acid can exist theoretically in four geometrically isomeric forms, *cis-cis*, *cis-trans*, *trans-cis*, and *trans-trans*. Of these, two have been obtained and it is probable, for reasons given later, that the other two will be unstable and difficult to isolate. Positional isomerism

* "The Third Isomeric (*cis-trans*-)Muconic Acid," *J.*, 1950, 2235, is regarded as Part I of this series.

is also possible in that all the mono-derivatives of the acids, such as the half-esters, can exist in two isomeric forms according to whether the *C*-methyl is β- or γ- to the ester group.* We have obtained and oriented isomerides of both types, geometrical and positional.

It will be convenient to deal with the preparation and general chemistry of the β-methylmuconic acids first, and their configuration secondly.

Preparation and Chemistry.—Important earlier work is that of Pauly, who found that 3-nitro-*p*-cresol with sulphuric acid gave (in addition to a nitrogenous compound, m. p. 206—207°) an unsaturated lactonic acid, $C_7H_8O_4$, m. p. 130°, derived from β-methylmuconic acid (Pauly, Gilmour, and Will, *Annalen*, 1914, **403**, 119; Pauly and Will, *ibid.*, 1918, **416**, 1). We have confirmed this preparation. The lactonic acid is converted by methanolic hydrogen chloride or more conveniently by diazomethane into a methyl ester, m. p. 37°. These compounds certainly have the structures (I) and (II) assigned to them by Pauly: the presence of the unsaturated γ-lactone ring followed from the alkaline hydrolysis to β-methyl-lævulic acid, and the position of the double bond from the results of oxidation (*loc. cit.*). The light absorption (see Table) confirms the Δ^{α}-structure (cf. Haynes and Jones, *J.*, 1946, 954), as also does the hydrogenation to a saturated lactone (XVIII).

Pauly and Will (*loc. cit.*) found that the lactonic ester (II) was isomerised by methanolic sodium methoxide to a β-methylmuconic half methyl ester, m. p. 125°, necessarily (δ)-methyl (α)-hydrogen β-methylmuconate (III). On hydrolysis this yielded β-methylmuconic acid, m. p. 170—171° (IV). We find that the m. p. of the acid varies with the rate of heating as with the muconic acids—presumably lactonisation occurs—and this doubtless accounts for the apparent discrepancies in the literature. Both the acid (IV) and the half-ester (III) with diazomethane yield the same methyl ester (V), the properties of which agree with those described by Pauly. This diester was also prepared from the acid (IV) with dilute methanolic hydrogen chloride, and it re-formed the β-methylmuconic acid (IV) on alkaline hydrolysis. The structure of the acid was confirmed by its catalytic hydrogenation to β-methyladipic acid (VI) and reduction by sodium amalgam to the known Δ^{β}-dihydro-β-methylmuconic acid (2-methylbut-2-ene-1 : 4-dicarboxylic acid) (VII). Partial esterification of the β-methylmuconic acid (IV) gave the half-ester (III).

Partial hydrolysis of methyl β-methylmuconate (V) with barium hydroxide gave the second half-ester (VIII), m. p. 170°. This product was reconverted into (V) by diazomethane, hydrolysed to the β-methylmuconic acid (IV) by alkali, and converted into β-methyladipic acid on hydrogenation followed by hydrolysis: its structure is therefore certain. The same half-ester (VIII) was obtained as a by-product from the reaction of the diester (V) with aqueous-methanolic ammonia, a reaction which gave mainly a half-amide ester (IX), m. p. 162°, as described by Pauly and Will (*loc. cit.*). Prolonged reaction of (V) afforded a third product, the diamide (X), which with nitrous acid yielded the parent acid (IV). The orientation of the half-amide ester (IX) was not determined by Pauly but now follows from its conversion with nitrous acid into the second acid ester (VIII). The positionally-isomeric half-amide ester (XI) (m. p. 141°) was obtained by treatment of the half-ester (III) with thionyl chloride (to yield the acid chloride) and then ammonia. Cautious hydrolysis of (XI) then afforded an acid amide (XII), m. p. 210—211°. The second acid amide (XIII) (m. p. 146—147°) was readily obtained by treatment of the half-ester (III) with ammonia. Both half-amides, (XII) and (XIII), with nitrous acid yielded the parent β-methylmuconic acid (IV).

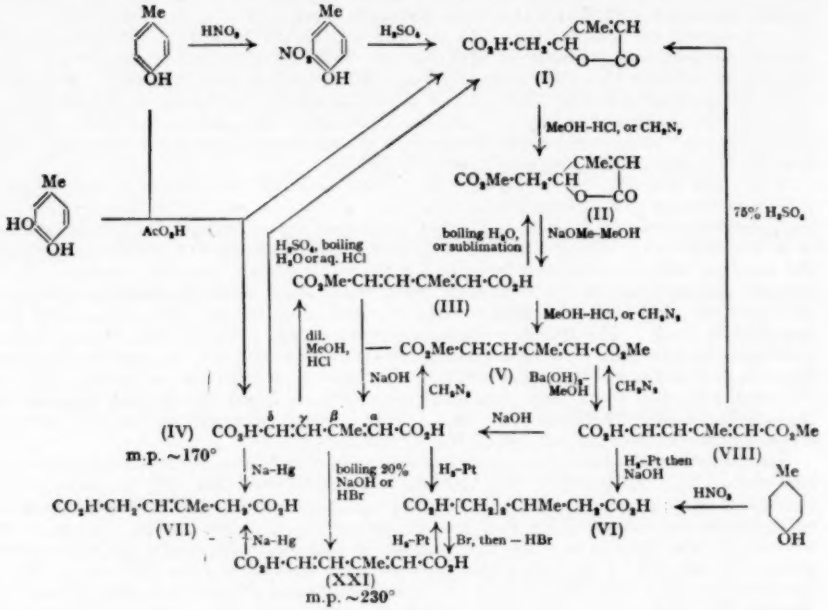
Lactonisation of the β-methylmuconic acid (IV) gave only the original lactonic acid (I) and no isomeride. There was an interesting and significant difference in the behaviour of the two isomeric half-esters, and of the two half-amides, under lactonising conditions. The α-acid δ-ester (III), m. p. 126° (with the *C*-methyl group β to carboxyl), readily changed back to the lactonic ester (II) from which it had been made. On the other hand the isomeride (VIII), m. p. 170°, with the δ-carboxyl group free (*C*-methyl β to carbomethoxyl), was stable to heat and could be sublimed unchanged. However, with 75% sulphuric acid, this stable acid ester (VIII) yielded the lactonic acid (I), evidently because hydrolysis of the ester liberated the α-carboxyl group, already shown to be capable of lactonisation. Again, the half-amide (XIII), m. p. 146°, with a free α-carboxyl group, readily cyclised to the lactonic amide (XIV), whereas

* These compounds have all been named as derivatives of *β*-methylmuconic acid: thus, *e.g.*, $CO_2Me\cdot\overset{trans}{CH}{:}\overset{cis}{CH}\cdot CMe{:}CH\cdot CO_2H$ is named (δ)-methyl (α)-hydrogen *β*-methyl-*cis*-*trans*-muconate; $CO_2Me\cdot\overset{trans}{CH}{:}\overset{cis}{CH}\cdot CMe{:}CH\cdot CO\cdot NH_2$ is *β*-methyl-*cis*-*trans*-muconic (α)-amide (δ)-methyl ester. The terms *cis* and *trans* are always given in positional order, *i.e.* the first cited refers to the lower-numbered double bond.

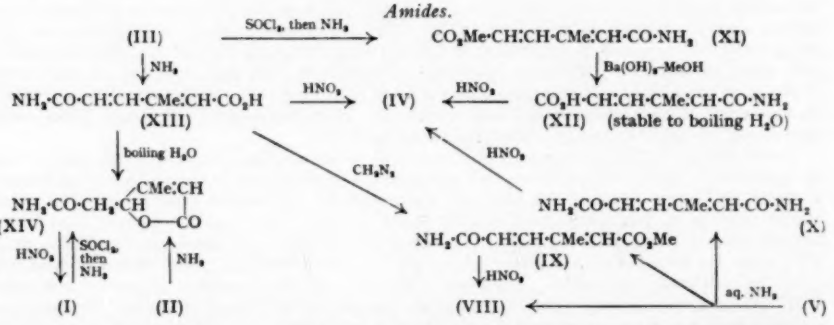
the isomeric half-amide (XII) (δ-carboxyl free) was unchanged. There is a simple stereochemical explanation for these facts which is discussed later.

The structure of the lactonic amide product (XIV) followed from the absorption spectrum, its conversion into the lactonic acid (I) by nitrous acid, and its synthesis, (*a*) from the lactonic acid with thionyl chloride and then ammonia, and (*b*) from the lactonic ester (II) with ammonia.

Lactones, acids, and esters.

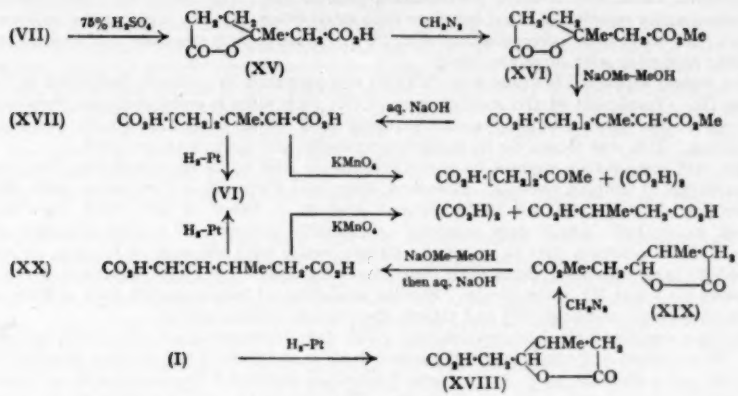


Amides.



It seemed of interest, also, to study the lactonisation of the available Δ^{β}-dihydro-β-methylmuconic acid (VII). This with 75% sulphuric acid readily afforded a lactonic acid product which appeared to be homogeneous. This acid is assigned the structure (XV) on the following evidence: fission of its ester (XVI) with sodium methoxide, and hydrolysis of the monounsaturated acid ester so produced, yielded a dihydro-β-methylmuconic acid (XVII) (reduced catalytically to β-methyladipic acid), which, since it gave oxalic and lævulic acids on oxidation, had the double bond in the αβ-position.

Dihydro-products.



Light-absorption data.

Compound		$\lambda_{max.}$, Å	ε	Solvent
R = OH		2260 •	3,900	EtOH
R = NH_2			5,880 at 2260 Å	EtOH
COR″·CH:CH·CMe:CH·COR′				
R′ = R″ = OH	*cis-trans*	2570 •	17,600	0·1M-NaOH
		2650	19,000	
	trans-trans	2590 •	20,100	0·1M-NaOH
		2650	22,400	
R′ = R″ = OMe	*cis-trans*	2580 •	21,000	EtOH
		2650	22,100	
	trans-trans	2590	26,700	EtOH
		2660	28,400	
R′ = R″ = NH_2	*cis-trans*	2270	11,200	EtOH
		2510 •	22,400	
		2580 •	24,600	
		2650	26,600	
	trans-trans	2260	11,200	EtOH
		2580 •	27,000	
		2650	30,600	
R′ = OH, R″ = OMe	*cis-trans*	2579 •	26,900	EtOH
		2650	28,000	
		2740 •	19,700	
R′ = OMe, R″ = OH	*cis-trans*	2570 •	22,100	EtOH
		2650	25,200	
R′ = OH, R″ = NH_2	*cis-trans*	2280	11,600	EtOH
		2510	14,700	
		2570 •	16,300	
		2640	18,000	
		2770	14,700	
R′ = NH_2, R″ = OH	*cis-trans*	2270	7,890	EtOH
		2500	24,800	
		2580	27,800	
		2640	27,800	
R′ = OMe, R″ = NH_2	*cis-trans*	2580 •	24,200	EtOH
		2650	25,800	
R′ = NH_2, R″ = OMe	*cis-trans*	2570 •	21,200	EtOH
		2650	24,400	
		2720 •	16,900	

• Inflection.

This Δ^{α}-acid (XVII) was identical (mixed m. p.) with an acid prepared for another purpose by Linstead, Lunt, and Weedon (forthcoming publication); this latter acid was obtained by the Reformatsky reaction of ethyl lævulate with ethyl bromoacetate, splitting the lactonic ester product [the ethyl ester corresponding with (XVI)] with sodium ethoxide, and hydrolysing the resultant half-ester with aqueous alkali.

The second saturated lactonic acid (XVIII) was prepared by catalytic reduction of Pauly's lactone (I). Treatment of the methyl ester (XIX) with sodium methoxide and then aqueous alkali gave the third dihydro-β-methylmuconic acid (XX) with the double bond in the γδ-position. This was shown by its oxidation to oxalic and methylsuccinic acids.

The next preparative method for β-methylmuconic acid to be examined was the peracetic acid oxidation of suitable phenols. Böeseken, Metz, and Pluim (*Rec. Trav. chim.*, **1935**, **54**, 345) had obtained from *p*-cresol a β-methylmuconic acid, m. p. 188·5°, in 20% yield, together with an acid, m. p. 124°, which they regarded as probably lactonic. We have obtained similar yields of these products (the m. p. of the former varies with the rate of heating, as already mentioned), and identified them with the compounds made by Pauly's method, having the structures (IV) and (I), respectively. Similar oxidation of homocatechol gave a little of the same β-methylmuconic acid (IV) and mainly the related lactonic acid (I).

We then examined the bromination and alkali dehydrobromination of β-methyladipic acid (VI). This yielded a second β-methylmuconic acid, m. p. 230° (XXI), with a dimethyl ester, m. p. 56°, and a diamide, m. p. 231°; these derivatives reafforded the parent acid on hydrolysis with alkali and nitrous acid, respectively. The structure was established by catalytic hydrogenation to β-methyladipic acid and amalgam reduction to Δ^{β}-dihydro-β-methylmuconic acid (VII). There can be little doubt that the acid (XXI) is identical with the high-melting acid [m. p. 235° (decomp.)] made by Stephen and Weizmann (*J.*, **1913**, **103**, 269) by dehydrobromination of αα′-dibromo-β-methyladipic ester with trimethylamine and with the material (m. p. 232°) made by Kuhn and Grundmann (*Ber.*, **1936**, **69**, 1757; **1937**, **70**, 1894) *via* the condensation of ββ-dimethyl- and β-ethyl-acrylic esters with oxalic ester.

Von Braun, Leistner, and Münch (*Ber.*, **1926**, **59**, 1950), using diethylamine for the dehydrobromination of dibromo-β-methyladipic acid, isolated a small quantity of a β-methylmuconic acid, m. p. 173°; this was most probably identical with Pauly's acid. The formation side by side of two stereoisomeric muconic acids by an analogous dehydrobromination has been observed by Farmer (*J.*, **1923**, **123**, 2531).

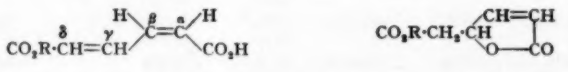
The β-methylmuconic acid, m. p. ~230°, is quite unchanged by sulphuric acid and by the conditions which convert the isomeric acid (IV), m. p. ~170°, into the lactonic acid (I).

Finally, the interconversion of the β-methylmuconic acids, (IV) and (XXI), was examined. When the acid, m. p. 170°, was heated for some hours with 20% aqueous sodium hydroxide it was converted into the acid of m. p. 230°, as described by Rinkes (*Rec. Trav. chim.*, **1929**, **48**, 1093). Hot concentrated hydrobromic acid also effected the same change, as reported by Pauly and Will (*loc. cit.*). The high-melting product of these changes was identical with the acid prepared from β-methyladipic acid, and the identity was confirmed by comparison of the dimethyl esters. Somewhat surprisingly, the low-melting acid showed no detectable change when its solutions were irradiated in the presence of traces of iodine. The high-melting acid was quite unchanged after similar treatment, and also after prolonged heating with alkali.

Configuration.—Light absorption provides no guide to configuration among muconic acids. The positions of the main absorption bands are practically the same for each isomer, there being no shift to shorter wave-lengths in the *cis*-forms. This would agree with the postulate that the absorbing systems have rather similar dimensions, corresponding with an *s-trans*-configuration for each of the stereoisomers, but the lack of " *cis*-shift " cannot be entirely so explained.

The lines of chemical evidence which can be used to assess the configuration of isomeric muconic acids are :

(1) *Ease of lactonisation.* A carboxyl group disposed *cis*- to the acrylic residue will lactonise readily, the *trans*-isomeride with difficulty if at all.



The determining factor in the reaction $A \longrightarrow B$ is the approach of the α-carboxyl to the γ-carbon atom, and this is affected by the geometry of the double bond αβ to carboxyl but not

by that of the γδ-double bond, or by that of the βγ-single bond (whether *s-cis* or *s-trans*). This applies to half-esters as well as to diacids.

(2) *Fission of unsaturated lactones.* The product of ring opening $B \longrightarrow A$, where R = alkyl, which is brought about by alkoxides, will be expected to have, initially, a *cis-trans*-configuration. The αβ-double bond must be *cis* in the lactone, and since it plays no part in the reaction, should remain *cis* in the product, unless other factors mentioned below [in (4)] operate. It has been shown that ring-opening of γ-dicarbethoxymethylenebutenolide under these conditions gives an undoubtedly *cis*-product (Eisner, Elvidge, and Linstead, *J.*, 1951, 1501). The γδ-double bond, which is formed in the reaction $B \longrightarrow A$, is considered to be *trans* by general analogy with such homogeneous elimination reactions and more particularly by analogy with related ester fissions now under study (cf. Elvidge, Linstead, Sims, and Orkin, *loc. cit.*).

(3) *Dehydrohalogenation.* In the same way we should expect double bonds formed by dehydrobromination of αα'-dibromoadipic acids to be predominantly *trans*.

(4) *Stability and interconversion.* The relative stabilities of the various isomerides, and the conditions required for their interconversion, will be some guide to configuration. The stabilities of substituted muconic acids will be affected by alkyl substitution and will therefore differ among the various homologous series. The most stable steric forms will be those in which there is the least intramolecular interference between substituent groups.

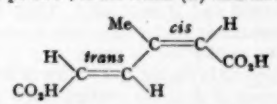
(5) *Fission of aromatic rings.* When a muconic acid is formed by fission of an aromatic ring under mild conditions, the carbon atoms will be expected to appear initially in a coiled phase with the bonds arranged *cis, s-cis, cis*. The central single bond will then most probably change to *s-trans*; whether the configuration about the double bonds will change will depend upon the conditions of reaction and the inherent stability of the *cis-cis*-isomer [as indicated under (4)].

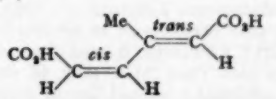
Additional considerations. These last points will also apply to unsaturated products derived by fission of lactones and other ring-compounds. Thus it is conceivable that the diene obtained from a reaction such as $B \longrightarrow A$ would not persist in its nascent *cis-trans*-form but would at once invert to the *trans-trans*-isomer. This could well be expected if the γ-carbon carried a bulky substituent. Reaction conditions alone might in some cases provoke inversion; the fission of a Δ^{α}-unsaturated lactone to a *trans*-product by aniline was observed by Eisner, Elvidge, and Linstead (*loc. cit.*). Likewise, a diene product isolated from the opening of a muconic anhydride (in which the butadiene bonds are necessarily arranged *cis, s-cis*, and *cis*) would not automatically have the *cis-cis*-configuration. The important case of β-methylmuconic anhydride, which gives rise to *cis-trans*-products, we discuss in the next paper.

No one of the foregoing criteria is sufficient by itself for the assignment of geometrical configuration to a muconic acid. Taken together, however, they provide powerful evidence, and, when applied to the β-methylmuconic acids and their derivatives, lead to the following conclusions:

(1) The acid (XXI), m. p. 230°, cannot be lactonised: hence it evidently has no *cis*-double bond. The acid (IV), m. p. 170°, readily forms a lactone; hence it has at least one *cis*-arrangement. As a second lactone (the *C*-methyl positional isomer) is not formed, it appears that the two double bonds are dissimilar, *i.e. cis* and *trans*. This conclusion is supported by the behaviour of the two half-esters and the two half-amides: the half-ester and half-amide which lactonise evidently have a *cis*-double bond adjacent to the free carboxyl group. As the other half-ester and half-amide fail to lactonise, the free carboxyl group is evidently in the unfavourable *trans*-position. The acid, m. p. 170°, is therefore *cis-trans*.

(2) The Δ^{α}-lactonic ester (II) with sodium alkoxide yields an acid ester of the acid, m. p. 170°. The *C*-methyl group is known to be on the β-carbon of the lactone ring so that the orientation of the half-ester product (and thence of the derived amide, etc.) is in no doubt. The *C*-methyl group will appear at one end of a *cis*-double bond in the β-methylmuconic product and hence the acid, m. p. 170°, is *cis-trans* (*C*) and not *trans-cis* (*D*).

(*C*) 



(*D*)

(3) As the acid, m. p. 230°, is formed from dehydrobromination reactions it should be *trans-trans*; Kuhn's method of preparation would also be expected to give a *trans*-product.

(4) To form an estimate of the relative stabilities of the various isomerides, scale models, based on covalent atomic radii, have been constructed. In accordance with current theory

concerning conjugated systems, the models have been given a planar arrangement. Interference between the various groups can then be observed in the following way :

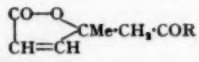
$$CO_2H\cdot\overset{\delta}{C}H{:}\overset{\gamma}{C}H\cdot\overset{\beta}{C}Me{:}\overset{\alpha}{C}H\cdot CO_2H$$

Steric form			Atoms or groups which interfere with one another
$\alpha\beta$	$\gamma\delta$	$\beta\gamma$	(possible minor effects are shown in brackets)
cis	*cis*	*s-cis*	α-carboxyl and δ-carboxyl
cis	*cis*	*s-trans*	β-methyl and δ-carboxyl
trans	*cis*	*s-cis*	[α-hydrogen and δ-carboxyl]
trans	*cis*	*s-trans*	β-methyl and δ-carboxyl, [β-methyl and α-carboxyl]
cis	*trans*	*s-cis*	[α-carboxyl and δ-hydrogen]
cis	*trans*	*s-trans*	none
trans	*trans*	*s-cis*	none
trans	*trans*	*s-trans*	[α-carboxyl and β-methyl]

The conclusion is drawn that β-methyl-*cis-trans*- and -*trans-trans*-muconic acid (and their esters, etc.) will be stable, and the other isomerides unstable. The fact that the several preparative methods lead only to two acids, either the acid, m. p. 170°, or the acid, m. p. 230°, is in agreement, and the conversion of the former into the latter acid is not inconsistent with it.

(5) The preparations from aromatic material are at first sight anomalous because they give rise to the acid, m. p. 170°, for which the *cis-trans*-configuration has been deduced. It is true that in the unsubstituted series it is possible to obtain the *cis-cis*-form by peracid oxidation of phenol, but the margin of stability of the product is slight and its conversion into the *cis-trans*-isomeride can be brought about even by very brief treatment with boiling water (Elvidge, Linstead, Sims, and Orkin, *loc. cit.*). Scale models show that the additional methyl group in β-methylmuconic acid gives rise to interference in the *s-trans*-form of the *cis-cis*-isomer and a lower stability than in *cis-cis*-muconic acid is to be expected. (There is of course serious interference in the *s-cis*-form.) We are, therefore, not disposed to regard the isolation of the acid (IV), m. p. 170°, from the oxidations of *p*-cresol and homocatechol as a very sound pointer to its steric configuration. The same remark applies to the isolation of the acid, m. p. 170°, from the reaction of β-methylmuconic anhydride with water, which we discuss in the next paper.

Supporting evidence for the *cis-trans*-formulation for the acid, m. p. 170°, is provided by the fact that it is easily lactonised to give *only one* lactonic acid ($A \longrightarrow B$). If it had the *cis-cis*-structure it ought to give two products—one lactonised on to the methylated β-carbon atom, the other on to the unmethylated γ-carbon atom. Moreover, both acid esters [(III) and (VIII)] and both acid amides [(XII) and (XIII)] should lactonise readily. Lactonisation involving the δ-carboxyl group, in the sense $E \longrightarrow F$, which is not observed, might be expected for two reasons.

(*E*) $CO_2H\cdot\overset{cis}{C}H{:}\overset{cis}{C}H\cdot CMe{:}CH\cdot COR$ (*F*) 

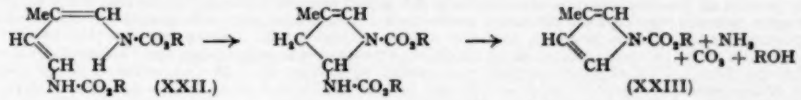
(where R = OH, OMe, NH_2)

First, the δ-carboxy-function of the β-methylmuconic system is more reactive than the α, irrespective of the geometrical configuration. This is shown by the facts that the acid (IV) is partially esterified to the (δ)-ester (α)-acid (III), that the diester (V) is partially hydrolysed to the (δ)-acid (α)-ester (VIII), that (V) reacts with ammonia to yield the (δ)-amide (α)-ester (IX), and that, as shown by Rinkes (*loc. cit.*), the higher-melting β-methylmuconic acid and its dimethyl ester, respectively, undergo partial esterification and partial hydrolysis in this same general sense.

Secondly, the lactonisation $E \longrightarrow F$ might be favoured by the *C*-methyl group. Lactonisation of pyroterebic and related acids is known to be assisted very greatly by the methyl substituents (Linstead, *J.*, 1932, 115; Linstead and Rydon, *ibid.*, 1933, 580) and the same has now been shown of Δ^{β}-dihydro-β-methylmuconic acid (VII), which yields only the lactone (XV), cyclisation having proceeded on to the methylated carbon.

Rinkes (*Rec. Trav. chim.*, 1929, **48**, 603), in addition to invoking the synthesis from aromatic material, adduced a second line of evidence in favour of a *cis-cis*-configuration for the acid, m. p. 170°. The derived diamide (X), on Hofmann degradation, yielded an isoprene diurethane (XXII) which in dilute sulphuric acid readily cyclised to 3-methylpyrrole-1-carboxylic ester (XXIII). In our view, however, these reactions are consistent with a *cis-trans*-structure. Scale models show that a *cis-trans*-isoprene urethane when in the *s-cis*-form (and cyclisation of

the *cis-cis*-isomer would also require intermediation of an *s-cis*-form) can cyclise readily by addition of the α-imino-group to the γδ-double bond: subsequent elimination of a urethane residue would then lead to the pyrrole (XXIII).



We therefore regard the two β-methylmuconic acids as having the following configurations:

	αβ	γδ
Acid, m. p. ~170° (IV)	*cis*	*trans*
Acid, m. p. ~230° (XXI)	*trans*	*trans*

The importance of this in relation to the configuration of the carotenoids is discussed in the following paper.

Experimental.

(M. p.s marked with an asterisk were taken from a bath at 165°, with the temperature rising 8°/minute. Other m. p.s were determined normally.)

γ-Carboxymethyl-β-methyl-Δ^α-butenolide (I) *and its Methyl Ester* (II).—3-Nitro-*p*-cresol (Schultz, *Ber.*, 1907, **40**, 4324) (200 g.) was treated with concentrated sulphuric acid (600 g.) according to the directions of Pauly, Gilmour, and Will (*loc. cit.*) to yield, besides a nitrogen-containing by-product (12 g.; needles, m. p. 206—206·5°, from ethanol), the lactonic acid (I) (170 g., 83%) which separated from ethanol–light petroleum (b. p. 40—60°), or from ethyl acetate, as prisms, m. p. 129—130° (Found: C, 53·8; H, 5·4. Calc. for $C_7H_8O_4$: C, 53·9; H, 5·2%).

Esterification of the acid (45 g.) with methanol (400 c.c.) containing 0·3% of hydrogen chloride gave the lactonic ester (II) (31 g., 63%), b. p. 180°/15 mm., m. p. 34—35° (needles), as described by Pauly, Gilmour, and Will (*loc. cit.*). An identical product (mixed m. p.) was obtained by brief treatment of the lactonic acid with excess of ethereal diazomethane and evaporation of the solution.

(δ)-*Methyl* (α)-*Hydrogen β-Methyl*-cis-trans-*muconate* (III).—The preceding lactonic ester (30 g.) was dissolved in methanolic sodium methoxide (from 4·6 g. of sodium and 60 c.c. of methanol), and the solution then concentrated under reduced pressure to two-thirds bulk and poured into cold 10% aqueous sulphuric acid (100 c.c.). The precipitated (δ)-methyl (α)-hydrogen β-methyl-*cis-trans*-muconate (III) (25 g., 83%) crystallised from benzene as needles, m. p. 126—127° (Found: C, 56·45; H, 6·0. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%). Pauly and Will (*loc. cit.*) record m. p. 127° for a similarly obtained product.

β-Methyl-cis-trans-*muconic Acid* (IV).—(δ)-Methyl (α)-hydrogen β-methyl-*cis-trans*-muconate (5 g.) was kept with 10% aqueous sodium hydroxide (25 c.c.) for 30 minutes at room temperature and the solution then acidified (Congo-red) with concentrated hydrochloric acid. The precipitated β-methyl-*cis-trans*-muconic acid (4·08 g., 90%) crystallised from ethanol as micro-needles, m. p. *ca.* 170° or 178—179° * (Found: C, 53·5; H, 5·3%; equiv., 77·2. Calc. for $C_7H_8O_4$: C, 53·8; H, 5·2%; equiv., 78). Pauly and Will (*loc. cit.*) give m. p. 170—171° (with gas evolution).

Variation of the M. P. of β-Methyl-cis-trans-*muconic Acid with Rate of Heating.*—

Initial temp. of bath.	Temp. rise.	M. p.
room temp.	8°/min.	172—173°
165°	8	178—179
165	15	190—191
165	1·5	167—167·5

Reduction.—(*a*) The preceding acid (500 mg.) in ethanol (10 c.c.) was hydrogenated in the presence of Adams's catalyst (50 mg.) (Hydrogen uptake: 170 c.c. at 25°/750 mm. Calc. for 2 double bonds: 161 c.c.) to yield β-methyladipic acid (0·4 g.; from nitric acid), m. p. and mixed m. p. 96—98°.

(*b*) Reduction of the acid (100 mg.) in 10% aqueous sodium hydroxide (6 c.c.) with 2·5% sodium amalgam (2·5 g.) for 30 minutes at room temperature gave, after filtration, acidification, and extraction with ether (3 × 10 c.c.), *trans*-Δ^β-dihydro-β-methylmuconic acid (VII) which crystallised from water as needles, m. p. 139—140°. Pauly and Will (*loc. cit.*) record m. p. 140—141°.

Methyl β-Methyl-cis-trans-*muconate* (V).—The half-ester (III) (10 g.) was kept for 24 hours with methanol (50 c.c.) containing 5% of dry hydrogen chloride. Evaporation of the solution under reduced pressure left methyl β-methyl-*cis-trans*-muconate (V) (9·7 g., 90%) which crystallised from aqueous methanol or light petroleum (b. p. 40—60°) as needles, m. p. 38—38·5° (Found: C, 58·8; H, 6·6. Calc. for $C_8H_{12}O_4$: C, 58·7; H, 6·6%). Pauly and Will (*loc. cit.*) give m. p. 38·5°.

Brief treatment of the half-ester (III) (0·1 g.) with ethereal diazomethane and evaporation of the solution gave the diester (0·1 g.), m. p. and mixed m. p. 37·5—38°.

The diester (m. p. and mixed m. p. 38—38·5°) was also prepared from β-methyl-*cis-trans*-muconic acid with ethereal diazomethane, and with 5% methanolic hydrogen chloride (10 parts by weight) for 48 hours at room temperature.

Hydrolysis of the diester (1·2 g.) in methanol with 10% aqueous sodium hydroxide (5·5 c.c.) for 1 hour at room temperature reafforded β-methyl-*cis-trans*-muconic acid (0·81 g., 80%) which separated from ethanol as micro-needles, m. p. and mixed m. p. 178—179°.*

Partial Esterification of β-Methyl-cis-trans-*muconic Acid: Formation of the Half-ester* (III).—A suspension of β-methyl-*cis-trans*-muconic acid (1·5 g.) in methanol (15 c.c.) containing 0·5% of dry hydrogen chloride was kept for 48 hours in the dark. Unchanged acid was filtered off, the filtrate evaporated under reduced pressure, and the residue extracted with boiling benzene (2 × 25 c.c.). Evaporation of the benzene afforded an oil which was extracted with saturated aqueous sodium hydrogen carbonate (5 c.c.). Th eaqueous extract was washed with ether (2 × 10 c.c.), acidified (Congo-red) with concentrated hydrochloric acid, and cooled in ice. (δ)-Methyl (α)-hydrogen β-methyl-*cis-trans*-muconate (0·23 g., 14%) separated; from benzene it formed needles, m. p. and mixed m. p. 126—127°.

Treatment of the product (0·1 g.) with ethereal diazomethane gave methyl β-methyl-*cis-trans*-muconate (needles from aqueous methanol), m. p. and mixed m. p. 37·5—38°.

Partial Hydrolysis of the Diester: Formation of (α)-*Methyl* (δ-)*Hydrogen* β-*Methyl*-cis-trans-*muconate* (VIII).—Methyl β-methyl-*cis-trans*-muconate (1·2 g.) was kept overnight with methanolic barium hydroxide (15·3 c.c.; 0·46N). The precipitate was dissolved in water, and the solution acidified. (α)-*Methyl* (δ)-*hydrogen* β-*methyl*-cis-trans-*muconate* (VIII) (0·9 g., 81%) crystallised from aqueous methanol as needles, m. p. 170° (Found: C, 56·6; H, 6·2%; equiv., 170. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%; equiv., 170·2).

Treatment of this half-ester with ethereal diazomethane reafforded methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 37—38°.

Treatment of the half-ester (200 mg.) with boiling sodium hydroxide solution (5 c.c.; 2N) for 30 minutes, and acidification, afforded β-methyl-*cis-trans*-muconic acid (110 mg.), m. p. and mixed m. p. 180—182°.*

Reduction of the half-ester (350 mg.) in ethanol (15 c.c.) with hydrogen and Adams's catalyst (hydrogen uptake: 55·0 c.c. at 21°/755 mm. Calc. for 2 double bonds: 49·2 c.c.) and hydrolysis of the oily product with boiling 10% sodium hydroxide (2 c.c.) for 30 minutes gave, on acidification, evaporation, and extraction with ethanol, β-methyladipic acid (200 mg.), m. p. and mixed m. p. 94—96°.

Amides derived from β-Methyl-cis-trans-*muconic Acid.*—(a) *The ester amide* (IX). Methyl β-methyl-*cis-trans*-muconate (V) (6 g.) was kept with methanol–aqueous ammonia (sp. gr. 0·88) mixture (150 c.c.; 1 : 1) for 4 days at 0°. The filtrate from unchanged ester was concentrated under reduced pressure to 20 c.c. (solid appeared), cooled, and filtered. Acidification of the filtrate gave (α)-methyl (δ)-hydrogen β-methyl-*cis-trans*-muconate (VIII) (0·5 g.), m. p. and mixed m. p. 167—168°. The solid was crystallised from ethanol yielding prisms, m. p. 162—163°, of β-methyl-*cis-trans*-muconic (α)-methyl ester (δ)-amide (IX) (4 g., 73%) (Found: C, 57·0; H, 6·7; N, 8·5. Calc. for $C_8H_{11}O_3N$: C, 56·8; H, 6·55; N, 8·3%). Pauly and Will (*loc. cit.*) record m. p. 161—162°

To the ester amide (IX) (1 g.) in 4% aqueous hydrochloric acid solution (60 c.c.) at room temperature, 10% sodium nitrite solution (10 c.c.) was added during 2 hours, with occasional shaking. The mixture was kept at 0° for 16 hours, and the solid then treated with aqueous sodium hydrogen carbonate. The insoluble material was unchanged ester amide (IX), m. p. and mixed m. p. 162—163°. Acidification of the alkaline extract gave (α)-methyl (δ)-hydrogen β-methyl-*cis-trans*-muconate (VIII) (100 mg., 10%) which crystallised from aqueous methanol as needles, m. p. and mixed m. p. 170°.

(b) *The diamide* (X). When methyl β-methyl-*cis-trans*-muconate (V) (4 g.) was kept with a methanol–aqueous ammonia (sp. gr. 0·88) mixture (50 c.c.; 1 : 1) for 10 days at room temperature, and the solution then evaporated under reduced pressure, β-methyl-*cis-trans*-muconamide (X) (3·3 g., 83%) was obtained, which crystallised from water as massive needles, m. p. 215—216° (Found: N, 18·2. Calc. for $C_7H_{10}O_2N_2$: N, 18·2%). Pauly and Will (*loc. cit.*) give m. p. 213—214°.

The finely powdered diamide (0·5 g.) was suspended in 10% aqueous hydrochloric acid (10 c.c.), and 20% sodium nitrite solution (4 c.c.) added during 4 hours, with occasional shaking. Crystallisation of the resulting solid from ethanol afforded micro-needles of β-methyl-*cis-trans*-muconic acid (0·35 g., 70%), m. p. and mixed m. p. 178—179°,* which with ethereal diazomethane gave methyl β-methyl-*cis-trans*-muconate (needles from aqueous methanol), m. p. and mixed m. p. 38·5°.

(c) *The amide ester* (XI). (δ)-Methyl (α)-hydrogen β-methyl-*cis-trans*-muconate (III) (0·8 g.; m. p. 127°) was heated under reflux with thionyl chloride (5 c.c.) for 15 minutes. Excess of reagent was removed under reduced pressure, and the residue added slowly to ammonia solution (2 c.c.; sp. gr. 0·88) at 0°. The precipitate (0·55 g., 69%) was washed with water and crystallised from ethanol yielding prisms, m. p. 141°, of β-*methyl*-cis-trans-*muconic* (α)-*amide* (δ)-*methyl ester* (XI) (Found: C, 56·7; H, 6·7; N, 8·4. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·55; N, 8·3%).

(d) *The amide acid* (XII). Treatment of the foregoing amide ester (XI) (0·3 g.) with methanolic barium hydroxide (4 c.c.; 0·79N) for 30 minutes at room temperature, dilution with water (4 c.c.), and acidification (hydrochloric acid), afforded β-*methyl*-cis-trans-*muconic* (α)-*amide* (δ)-*acid* (XII) (0·15 g., 52%) which crystallised from water as needles, m. p. 210—211° (Found: C, 54·05; H, 6·0; N, 9·3. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%).

To this amide acid (0·2 g.), suspended in water (5 c.c.) containing a few drops of concentrated hydrochloric acid, 10% aqueous sodium nitrite (2 c.c.) was added during 6 hours with occasional shaking. The resulting crude β-methyl-*cis-trans*-muconic acid (0·125 g., 62%), m. p. 168—172° *, was treated with diazomethane in ether, and the product crystallised from aqueous methanol giving methyl β-methyl-*cis-trans*-muconate (V) as needles, m. p. and mixed m. p. 37—38°.

(e) *The acid amide* (XIII). After (δ)-methyl (α)-hydrogen β-methyl-*cis-trans*-muconate (III) (2 g.) had been kept with aqueous ammonia (10 c.c.; sp. gr. 0·88) for 2 days, the excess of ammonia was

removed under reduced pressure and the solution acidified (hydrochloric acid). *β-Methyl*-cis-trans-*muconic* (α)-*acid* (δ)-*amide* (XIII) (0·9 g., 49%) crystallised slowly, and was recrystallised from methanol giving needles, m. p. 146—147° (Found: C, 54·5; H, 6·1; N, 8·7. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%).

Reaction of this acid amide (200 mg.), suspended in ether, with an excess of ethereal diazomethane afforded the methyl ester amide (IX) which formed prisms, m. p. 159—160°, from ethanol. A mixture with authentic material had m. p. 162—163°.

Treatment of the acid amide (XIII) (200 mg.), as a fine suspension in water (2 c.c.) containing concentrated hydrochloric acid (several drops), with 10% aqueous sodium nitrite (2 c.c.) during 6 hours at room temperature gave a sparingly soluble acid (90 mg., 45%), m. p. 172—174° * undepressed by β-methyl-*cis-trans*-muconic acid. Reaction of the crude product with ethereal diazomethane, and crystallisation from aqueous methanol yielded methyl β-methyl-*cis-trans*-muconate as needles, m. p. and mixed m. p. 37°.

Lactonisation Experiments.—(a) *Cyclisation of β-methyl*-cis-trans-*muconic acid.* (i) The acid (1 g.) was kept with 75% sulphuric acid (2 c.c.) overnight, and the solution added to crushed ice (40 g.), and extracted with ether for 48 hours. On evaporation of the ether, γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (I) (0·73 g., 73%) was obtained, which crystallised from ethanol–benzene as prisms, m. p. and mixed m. p. 129—130°. (ii) After β-methyl-*cis-trans*-muconic acid (2 g.) had been heated under reflux with water (20 c.c.) containing concentrated hydrochloric acid (several drops) for 12 hours, γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (1·8 g., 90%) was similarly isolated (m. p. and mixed m. p. 127—128°). (iii) By heating β-methyl-*cis-trans*-muconic acid (2 g.) with water (20 c.c.) under reflux for 24 hours, and extracting the solution with ether for 48 hours, the lactonic acid (I) (1·7 g., 85%) was again obtained (m. p. and mixed m. p. 127—128°).

(b) *Lactonisation of* (δ)-*methyl* (α)-*hydrogen β-methyl*-cis-trans-*muconate.* (i) The half-ester (III) (1 g.) was heated under reflux with water (20 c.c.) for 2 hours, and the solution cooled and extracted with ether (2 × 20 c.c.). After being washed with saturated aqueous sodium hydrogen carbonate (20 c.c.), the ether was evaporated and γ-carbomethoxymethyl-β-methyl-Δ^{α}-butenolide (II) (0·9 g., 90%) obtained as an oil, b. p. 175—176°/12 mm. (ii) Distillation of (δ)-methyl (α)-hydrogen β-methyl-*cis-trans*-muconate (III) (2 g.) under reduced pressure also afforded the lactonic ester (II), b. p. 170—173°/12 mm., m. p. and mixed m. p. 34—35°, in 65% yield. Some dark gum remained in the distilling flask.

(c) *Attempts to lactonise* (α)-*methyl* (δ)-*hydrogen β-methyl*-cis-trans-*muconate.* (i) After the half-ester (VIII) (100 mg.) had been heated with water (10 c.c.) under reflux for 48 hours, 90% was recovered directly as long needles (90 mg.), m. p. and mixed m. p. 170—171°. The remainder (10 mg.), m. p. and mixed m. p. 168—169°, was recovered by evaporation of the filtrate. (ii) The half-ester (VIII) (1 g.) when heated at 220°/15 mm. slowly sublimed as prismatic needles (0·7 g., 70%), m. p. 165—167°, and m. p. 165—168° when mixed with the starting material. (iii) The half-ester (VIII) (0·7 g.) was heated at 220° for 2 hours and the pressure then reduced to 15 mm. A sublimate of needles appeared (0·35 g., 50%) which when recrystallised from hot water had m. p. 169—170°, alone and in admixture with the starting material. A brown-coloured resin remained in the distilling flask. (iv) A mixture of the half-ester (VIII) (0·5 g.) and 75% sulphuric acid (10 c.c.) was kept for 24 hours, then poured on ice (45 g.), and the solution extracted with ether for 24 hours to yield γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (0·2 g., 43%) which separated from ethanol–light petroleum (b. p. 40—60°) as prisms, m. p. and mixed m. p. 127—129°.

(d) *Behaviour of the two acid amides.* (i) β-Methyl-*cis-trans*-muconic (α)-acid (δ)-amide (XIII) (0·5 g.) was heated under reflux with water (10 c.c.) for 2 hours, and the solution evaporated to dryness. From ethanol, the amide of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (XIV) (0·45 g., 90%) formed needles, m. p. 150—151° undepressed by authentic material (described below). (ii) The (α)-amide (δ)-acid (XII) (50 mg.) was recovered unchanged after being heated under reflux with water (5 c.c.) for 3 hours. The only changed material obtained by heating the (α)-amide (δ)-acid (XII) at above the m. p. was a resinous substance.

The Amide of γ-Carboxymethyl-β-methyl-Δ^{α}*-butenolide.*—(i) γ-Carboxymethyl-β-methyl-Δ^{α}-butenolide (I) (5 g.) was heated under reflux with thionyl chloride (20 c.c.). After 30 minutes, excess of the reagent was removed under reduced pressure, and the residue, in dry ether (50 c.c.), was added during 20 minutes, with stirring, to ether (250 c.c.) through which dry ammonia gas was being passed. The solid was dissolved in water (100 c.c.), and the solution extracted with ether for 48 hours to yield the *amide* of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (XIV) (4·3 g., 96%) which crystallised from ethanol as needles, m. p. 151° (Found: C, 54·3; H, 5·9; N, 9·1. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%). (ii) A solution of the lactonic ester (II) (1 g.) in methanol–ammonia (sp. gr. 0·88) (10 c.c.; 1 : 1) was kept for 2 days, then evaporated under reduced pressure. From ethanol, the lactonic amide (XIV) formed needles (0·8 g., 80%), m. p. and mixed m. p. 145—148°.

Treatment of the lactonic amide (1 g.) in 10% hydrochloric acid (10 c.c.) with 10% sodium nitrite solution (8 c.c.), added during 6 hours at room temperature, afforded (after constant ether-extraction for 48 hours) γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (I) which crystallised from ethanol as needles (0·25 g., 25%), m. p. and mixed m. p. 126—127°.

Dihydro-β-methylmuconic Acids and Related Lactones.—*trans*-Δ^{β}-Dihydro-β-methylmuconic acid (2-methyl-*trans*-but-2-ene-1 : 4-dicarboxylic acid) (VII) was obtained in 87% yield by amalgam reduction of (δ)-methyl (α)-hydrogen β-methyl-*cis-trans*-muconate (III) (13 g.) in sodium hydroxide solution (80 c.c.; 0·1N), according to Pauly and Will's directions (*loc. cit.*); the dihydro-acid separated from water as needles, m. p. 140—141° (Found: C, 53·25; H, 6·55. Calc. for $C_7H_{10}O_4$: C, 53·1; H, 6·4%).

Reduction of the Δ^{β}-dihydro-acid (450 mg.) with hydrogen and Adams's catalyst (hydrogen uptake: 72·0 c.c. at 18°/755 mm. Calc. for 1 double bond: 68·5 c.c.) afforded β-methyladipic acid, m. p. 95—96° and mixed m. p. 95—97°.

γ-Carboxymethyl-γ-methylbutanolide (XV). *trans*-Δ^{β}-Dihydro-β-methylmuconic acid (VII) (5·5 g.) was kept with 75% sulphuric acid (60 c.c.) at room temperature for 48 hours. The solution was poured on crushed ice (200 g.) and extracted with ether for 48 hours to yield *γ-carboxymethyl-γ-methylbutanolide* (XV) (4·2 g., 76%) which slowly crystallised, and then formed needles, m. p. 60—63°, from ether–light petroleum (b. p. 40—60°) (Found: C, 53·5; H, 6·4%; equiv., 156·2; hydrolysis-equiv., 78·8. $C_7H_{10}O_4$ requires C, 53·1; H, 6·4%; equivs., 158·1, 79·05)

γ-Carbomethoxymethyl-γ-methylbutanolide (XVI). This *lactone*, b. p. 142°/10 mm., n_D^{18} 1·4573 (Found: C, 55·6; H, 6·9. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%) was obtained in 73% yield from the preceding lactonic acid (2·5 g.) and ethereal diazomethane

trans-Δ^{α}-*Dihydro-β-methylmuconic Acid* (2-*Methyl*-trans-*but*-1-*ene*-1 : 4-*dicarboxylic Acid*) (XVII).—(a) *Preparation.* To the preceding lactonic ester (XVI) (1·6 g.) in methanol (2 c.c.), methanolic sodium methoxide (2·7 c.c.; equivalent to 0·214 g. of sodium) was added, and after 20 minutes the solution was evaporated under reduced pressure and the residue taken up in water (10 c.c.). The solution was acidified (hydrochloric acid) and the resulting mixture extracted with ether (3 × 10 c.c.). Back extraction of the latter with saturated aqueous sodium hydrogen carbonate (2 × 20 c.c.), acidification of the ether-washed aqueous extract, and isolation with ether afforded an oil, presumed to be mainly methyl hydrogen *trans*-Δ^{α}-dihydro-β-methylmuconate (1·3 g.) (Found: equiv., 171·2. $C_9H_{12}O_4$ requires equiv., 172·2). Hydrolysis of this half-ester (1 g.) by heating it under reflux with 10% aqueous sodium hydroxide (8 c.c.) for 15 minutes, acidifying the solution and cooling it to 0° for several hours, yielded a crude acid (0·85 g.), m. p. 125—151°. Fractional crystallisation from water and from ethyl acetate–benzene gave trans-Δ^{α}-*dihydro-β-methylmuconic acid* (2-*methyl*-trans-*but*-1-*ene*-1 : 4-*dicarboxylic acid*) (XVII) (0·29 g., 31%) as needles, m. p. 158—161° (Found: C, 53·4; H, 6·5. $C_7H_{10}O_4$ requires C, 53·1; H, 6·4%). Hydrolysis of the half-ester (160 mg.) by treatment with 10% aqueous sodium hydroxide (1 c.c.) for 30 minutes at room temperature, and acidification of the solution, gave a similar crude product. Repeated crystallisation (as before) then afforded the Δ^{α}-acid, m. p. and mixed m. p. 158—161°.

The acid prepared by Linstead, Lunt, and Weedon, as mentioned earlier, had m. p. 157—160° and a mixture with the preceding Δ^{α}-acid had m. p. 158—161°.

(b) *Reduction.* The Δ^{α}-acid (XVII) (158 mg.) in ethanol (10 c.c.) was hydrogenated in the presence of Adams's catalyst (hydrogen uptake: 24·5 c.c. at 20°/768 mm. Calc. for 1 double bond: 24·4 c.c.) to yield β-methyladipic acid, m. p. and mixed m. p. 94—95°.

(c) *Oxidation.* To an ice-cold solution of the Δ^{α}-acid (300 mg.) in saturated aqueous sodium hydrogen carbonate (10 c.c.), 2% potassium permanganate solution (30·8 c.c.; 3 atoms of O) was added, with stirring, during 2 hours. The manganese dioxide was filtered off and washed with hot water (10 c.c.), and the combined filtrate acidified (hydrochloric acid) and ether-extracted for 24 hours. Evaporation of the ether afforded a mixture of a solid with an oily acid. When crystallised from water, the solid acid (98 mg., 41%) had m. p. 99—100°, undepressed by oxalic acid dihydrate. From the oil (160 mg., 72%) a 2 : 4-dinitrophenylhydrazone and a semicarbazone were prepared, which had m. p.s 204—205° and 184°, respectively, not depressed by the corresponding derivatives of lævulic acid.

γ-Carboxymethyl-β-methylbutanolide (XVIII). The unsaturated lactonic acid (I) (3 g.) in ethanol (20 c.c.) was reduced with hydrogen and Adams's catalyst (hydrogen uptake: 496 c.c. at 20°/755 mm. Calc. for 1 double bond: 483 c.c.) to yield *γ-carboxymethyl-β-methylbutanolide* (2·7 g., 93%) which crystallised from ether–light petroleum (b. p. 40—60°) as stout prisms, m. p. 90—91° (Found: C, 53·4; H, 6·4%; equiv., 157·5; hydrolysis-equiv., 78·6. $C_7H_{10}O_4$ requires C, 53·1; H, 6·4%; equivs., 158·1, 79·05).

γ-Carbomethoxymethyl-β-methylbutanolide (XIX), obtained in 74% yield by treating the preceding lactonic acid (XVIII) (2·7 g.) with ethereal diazomethane, had b. p. 154°/10 mm., n_D^{18} 1·4576 (Found: C, 55·6; H, 7·0. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%).

trans-Δ^{γ}-*Dihydro-β-methylmuconic Acid* (3-*Methyl*-trans-*but*-1-*ene*-1 : 4-*dicarboxylic Acid*) (XX).—(a) *Preparation.* The preceding saturated lactonic ester (XIX) (0·4 g.) in methanol (1 c.c.) was treated with methanolic sodium methoxide (1 c.c.; equivalent to 0·08 g. of sodium). After 20 minutes, the solution was diluted with water (12 c.c.), acidified (hydrochloric acid), and extracted with ether (3 × 10 c.c.) to yield an oil which was heated under reflux with 10% aqueous sodium hydroxide (3 c.c.) for 30 minutes. The hydrolysate was acidified (hydrochloric acid) and cooled to 0°. trans-Δ^{γ}-*Dihydro-β-methylmuconic acid* (3-*methyl*-trans-*but*-1-*ene*-1 : 4-*dicarboxylic acid*) (XX) (0·21 g., 54%) crystallised from water as needles, m. p. 129° (Found: C, 53·3; H, 6·6. $C_7H_{10}O_4$ requires C, 53·1; H, 6·4%).

(b) *Reduction.* Hydrogenation of the Δ^{γ}-acid (210 mg.) in methanol (10 c.c.) in the presence of Adams's catalyst (hydrogen uptake: 36 c.c. at 20°/764 mm. Calc. for 1 double bond: 33 c.c.) yielded β-methyladipic acid (200 mg.), m. p. and mixed m. p. 95—97°.

(c) *Oxidation.* 2% Aqueous potassium permanganate (37 c.c.; 4 atoms of O) was added during 2 hours to a stirred solution of *trans*-Δ^{γ}-dihydro-β-methylmuconic acid (270 mg.) in saturated aqueous sodium hydrogen carbonate (5 c.c.). The filtrate from the manganese dioxide was acidified and extracted with ether for 12 hours. Evaporation of the ether gave a sticky solid which was extracted with hot benzene (3 × 10 c.c.). On concentration of the benzene extract, methylsuccinic acid (150 mg., 67%) crystallised as needles, m. p. 106—107° and mixed m. p. 106—108°. The residue from the benzene extraction was taken up in hot water. On concentration and cooling, oxalic acid dihydrate (70 mg., 29%) was obtained, m. p. and mixed m. p. 100—101°.

Peracetic Acid Oxidation of p-*Cresol* (cf. Böeseken, Metz, and Pluim, *loc. cit.*).—A solution of *p*-cresol (35 g.) in 13% peracetic acid (600 g.) was kept for 14 days in the dark, and the crystalline precipitate (3 g., 6%) recrystallised from ethanol to yield β-methyl-*cis-trans*-muconic acid as micro-needles, m. p. and mixed m. p. 178—179° • (Found: C, 53·8; H, 5·2. Calc. for $C_7H_8O_4$: C, 53·9; H, 5·2%). The

product was further characterised by reaction with ethereal diazomethane to give methyl β-methyl-*cis-trans*-muconate (needles from aqueous methanol), m. p. and mixed m. p. 38—38·5°.

The acetic acid filtrate was concentrated to a small bulk under reduced pressure, whereupon γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (I) (29 g., 56%) separated; recrystallised from ethanol–benzene, the lactonic acid had m. p. and mixed m. p. 129—130° (Found: C, 53·9; H, 5·3. Calc. for $C_7H_8O_4$: C, 53·9; H, 5·2%). Esterification of the lactonic acid (14 g.) with boiling 0·3% methanolic hydrogen chloride (50 c.c.) for 2 hours gave γ-carbomethoxymethyl-β-methyl-Δ^{α}-butenolide (II) (11 g., 73%), b. p. 179°/11 mm., m. p. and mixed m. p. 35°.

Peracetic Acid Oxidation of Homocatechol.—Homocatechol (10 g.) was added slowly, with cooling, to 13% peracetic acid (250 c.c.), and the solution kept for 14 days in the dark. β-Methyl-*cis-trans*-muconic acid (50 mg., 4%) was precipitated, and on crystallisation from ethanol formed micro-needles, m. p. and mixed m. p. 178—179°.* Treatment with ethereal diazomethane yielded methyl β-methyl-*cis-trans*-muconate (needles from aqueous methanol), m. p. and mixed m. p. 38—38·5°. Concentration of the acetic acid filtrate gave γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (I) (7·8 g., 61%), m. p. and mixed m. p. 129—130°.

β-Methyl-trans-trans-*muconic Acid.*—(a) *Preparation.* To a mixture of 50% nitric acid (402 g.) and ammonium vanadate (0·2 g.) at 95°, 4-methyl*cyclo*hexanol (100 g.) was added at such a rate that the temperature kept at 55—60°. Next day, β-methyladipic acid (90 g., 65%), m. p. 96—98°, was collected (cf. D.R.P. 473,960; cf. also the preparation of the lower homologue, *Org. Synth.*, Coll. Vol. II, 18). The acid (65 g.) was cautiously treated with thionyl chloride (120 g.), the mixture heated under reflux on the steam-bath to complete the reaction, and excess of thionyl chloride then distilled under reduced pressure. To the crude acid chloride, iodine (a few crystals) was added, and, with continued heating on the steam-bath, dry bromine (150 g.) was run in during 12 hours. After being heated for 2 hours longer, the reaction product was cooled and slowly added to ice-cooled anhydrous ethanol (360 c.c.). The solution was poured into water (500 c.c.), the oil separated, and the aqueous layer extracted with ether (2 × 250 c.c.). The oil and ethereal extracts were combined and washed with 5% aqueous sodium carbonate (250 c.c.), 5% aqueous sodium hydrogen sulphite (250 c.c.), and water (250 c.c.). After the solution had been dried (Na_2SO_4), the ether was distilled, and the crude ethyl αδ-dibromo-β-methyladipate (138 g., 91%) added slowly to a boiling solution of potassium hydroxide (360 g.) in methanol (600 c.c.), which was heated for 1 hour longer and then cooled. The potassium salts were collected, dissolved in water (charcoal), and the solution acidified (Congo-red) with concentrated hydrochloric acid. β-Methyl-*trans-trans*-muconic acid (XXI) (5·5 g., 8·5%) slowly separated, and from hot water crystallised as needles, m. p. 229—231° (Found: C, 54·0; H, 5·2%; equiv., 77·2. Calc. for $C_7H_8O_4$: C, 53·9; H, 5·2%; equiv., 78·0) (cf. the preparation of the lower homologue due to Ingold, *J.*, 1921, **119**, 951).

(b) *Reduction.* The *trans-trans*-acid (500 mg.) with hydrogen and Adams's catalyst (hydrogen uptake: 172·5 c.c. at 25°/754 mm. Calc. for 2 double bonds: 160·5 c.c.) gave β-methyladipic acid, m. p. and mixed m. p. 96—98°.

Reduction of the *trans-trans*-acid (100 mg.) with 2·5% sodium amalgam (as for the *cis-trans*-isomer) gave *trans*-Δ^{β}-dihydro-β-methylmuconic acid, m. p. 139—140°.

(c) *Methyl ester.* The *trans-trans*-acid (1 g.) with ethereal diazomethane yielded methyl β-methyl-*trans-trans*-muconate (1 g.) which crystallised from aqueous methanol, and from light petroleum (b. p. 40—60°), as needles, m. p. 56° (Found: C, 58·9; H, 6·6. Calc. for $C_8H_{12}O_4$: C, 58·7; H, 6·6%).

The ester (0·3 g.) was dissolved in 10% aqueous sodium hydroxide (25 c.c.) with the aid of methanol. After 1 hour at room temperature, the solution was acidified (hydrochloric acid) (Congo-red), and the precipitate crystallised from water. β-Methyl-*trans-trans*-muconic acid (0·18 g., 41%) was obtained, m. p. and mixed m. p. 230°.

(d) *Amide.* The preceding ester (900 mg.) was kept with methanol–aqueous ammonia (sp. gr. 0·88) (15 c.c., 1 : 1) for 7 days. *β-Methyl*-trans-trans-*muconamide* (220 mg., 29%) separated from water as stout needles, m. p. 230—231° (Found: C, 54·5; H, 6·6; N, 17·9. $C_7H_{10}O_2N_2$ requires C, 54·5; H, 6·5; N, 18·2%).

The amide (300 mg.) was suspended in 30% hydrochloric acid (3 c.c.) and treated with 20% aqueous sodium nitrite (1 c.c.) during 3 hours. The solid was recrystallised from hot water yielding β-methyl-*trans-trans*-muconic acid (120 mg., 40%), m. p. and mixed m. p. 230—231°, which with ethereal diazomethane afforded the dimethyl ester, m. p. and mixed m. p. 53—54°.

(e) *Attempted lactonisation.* When the *trans-trans*-acid (0·5 g.) was kept with 80% sulphuric acid (5 c.c.) for 48 hours, the solution poured on crushed ice (10 g.), and the precipitate crystallised from hot water, β-methyl-*trans-trans*-muconic acid (0·45 g., 90%) was recovered, m. p. and mixed m. p. 230°. Extraction of the filtrate with ether for 24 hours yielded only a small quantity of *trans-trans*-acid, m. p. 225—227° undepressed by authentic material.

After being heated under reflux with 10% hydrochloric acid (10 c.c.) for 24 hours, β-methyl-*trans-trans*-muconic acid (0·5 g.) was recovered (0·46 g., 92%), m. p. and mixed m. p. 229—230°.

Isomerisation Experiments.—(a) *Conversion of β-methyl*-cis-trans- *into* -trans-trans-*muconic acid.* (i) The *cis-trans*-acid (1 g.) was heated under reflux with 20% sodium hydroxide (10 c.c.) for 4 hours. On acidification of the solution, β-methyl-*trans-trans*-muconic acid (0·7 g., 70%) was obtained, m. p. and mixed m. p. 223—227°, which on reaction with ethereal diazomethane gave fine needles (from aqueous methanol) of methyl β-methyl-*trans-trans*-muconate, m. p. and mixed m. p. 55—56°. (ii) The *cis-trans*-acid (1 g.) was heated at 100° for 3 hours with 48% aqueous hydrogen bromide (10 c.c.), and the solution evaporated under reduced pressure. Recrystallisation of the residue from water gave β-methyl-*trans-trans*-muconic acid (0·45 g., 45%), m. p. and mixed m. p. 228—229°, additionally characterised by

reaction with ethereal diazomethane to yield methyl β-methyl-*trans-trans*-muconate, m. p. and mixed m. p. 55—56°.

(b) *Stereochemical stability of β-methyl*-cis-trans-*muconic acid.* (i) A solution of the *cis-trans*-acid (1 g.) in ethanol (10 c.c.) containing iodine (one small crystal) was exposed to ultra-violet light (from a Hanovia lamp) for 1 hour, then evaporated under reduced pressure. From ethanol, only β-methyl-*cis-trans*-muconic acid was obtained, m. p. and mixed m. p. 178—179° *, which with diazomethane in ether yielded methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38°. (ii) The *cis-trans*-acid was recovered after being kept in methanol containing sulphur dioxide and a trace of hydrogen chloride.

(c) *Stereochemical stability* of trans-trans-*β-methylmuconic acid.* (i) The *trans-trans*-acid (1 g.) in ethanol (10 c.c.) containing a trace of iodine underwent no change on being irradiated with ultra-violet light as above. The solution was evaporated and the residue treated with ethereal diazomethane. Methyl β-methyl-*trans-trans*-muconate was obtained, m. p. and mixed m. p. 56°, after being crystallised from aqueous methanol. (ii) The *trans-trans*-acid (1 g.) was heated under reflux with 30% aqueous sodium hydroxide (20 c.c.) for 4 hours, and the solution acidified (hydrochloric acid). β-Methyl-*trans-trans*-muconic acid (0·62 g., 62%) was recovered, m. p. and mixed m. p. 230—231°. The filtrate was heated under reflux for 3 hours (in order to lactonise any *cis-trans*-acid which might have been produced) and the solution extracted with ether for 24 hours. Evaporation of the ether gave a residue, m. p. 221—225° not depressed by β-methyl-*trans-trans*-muconic acid.

We thank Dr. E. A. Braude for the light-absorption data, and the Ministry of Education for a grant (to P. S.).

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[*Received, July 17th*, 1951.]

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747. *Polyene Acids. Part III. A Reinvestigation of Karrer's β-Methylmuconic Acid.*

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We have confirmed Karrer's preparation of β-methyl-*cis-cis*-muconic anhydride (I) but find that its reaction with water leads to β-methyl-*cis-trans*-muconic acid, and not the *cis-cis*-isomer as claimed. With methanol, the anhydride yields a mixture of (α)-methyl (δ)-hydrogen and (δ)-methyl (α)-hydrogen β-methyl-*cis-trans*-muconates, whilst with ammonia the amide of Pauly's lactonic acid (VI) is given together with the two half amides of β-methyl-*cis-trans*-muconic acid (as their ammonium salts). No evidence for the formation of *cis-cis*-products could be obtained. Karrer's criticism of the Pauling–Zechmeister theory of stereoisomerism in the carotenoids thus loses its basis.

A PREPARATION of β-methylmuconic anhydride (I) was recently described by Karrer, Schwyzer, and Neuwirth (*Helv. Chim. Acta*, 1948, **31**, 1210). They claimed that this anhydride—necessarily a *cis-cis*-compound—on brief treatment with boiling water afforded the *cis-cis*-isomer of β-methylmuconic acid. No further evidence for the configuration of the product was provided. On the basis of this apparent isolation of an isoprene derivative in the *cis-cis*-form, Karrer *et al.* criticised the concepts which underlie the Pauling–Zechmeister theory of stereoisomerism in the carotenoids.

Karrer's preparation was seemingly in conflict with our conclusions concerning the stereochemistry of β-methylmuconic acid, which are set forth in the preceding paper. The extreme rapidity with which the lower homologue, *cis-cis*-muconic acid, is inverted by boiling water to the *cis-trans*-isomer (Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235) also cast considerable doubt on Karrer's assignment of the *cis-cis*-configuration to his β-methylmuconic acid. We have accordingly reinvestigated Karrer's work.

β-Methylmuconic Anhydride.—There seems no doubt that the product of oxidation of 4-methyl-1 : 2-benzoquinone with monoperphthalic acid (Karrer, Schwyzer, and Neuwirth, *loc. cit.*) has the cyclic structure (I). This low-melting volatile compound is neutral and polymerises readily. It reacts with water to yield a diene-dicarboxylic acid from which β-methyladipic acid is formed by hydrogenation. The anhydride itself, however, is resistant

to catalytic reduction, and in this respect resembles dimethylmaleic and citraconic anhydrides (Hancock, Linstead, and J. F. Smith, unpublished observations): maleic anhydride is likewise a powerful catalyst poison (Braude, Linstead, and Mitchell, unpublished work). Also consistent with the cyclic structure (I) are the light-absorption characteristics. The maxima shown by the anhydride (at 2650 and 2800 Å) are shifted by ~150 Å to longer wave-lengths as compared with those of muconic and β-methylmuconic acids (max. at 2510—2650 Å). In the pair maleic acid (or ester) and anhydride the shift is ~110 Å (Wassermann and Smakula, *Z. physikal. Chem.*, 1931, **155**, 366; Sörensen, *Annalen*, 1941, **546**, 57), whilst for 1-methylbutadiene and *cyclo*pentadiene the shift is ~200 Å (Braude, *Ann. Reports*, 1945, **42**, 105).

The β-Methylmuconic Acid derived from the Anhydride.—Karrer *et al.* (*loc. cit.*) reported that the melting point of the β-methylmuconic acid derived from the anhydride (I) and water varied with the rate of heating but was 170—171·5° under specified conditions. The acid was regarded by these authors as probably identical with the "lower-melting β-methylmuconic acid" described in the older literature. We find by direct comparison that this is correct; not so their stereochemical conclusions.* The β-methylmuconic acid (II) derived from the anhydride (I) and water is identical with the acid obtained by Pauly and Will's method (*Annalen*, 1918, **416**, 1) from the lactone (V), or from the peracetic acid oxidation of either homocatechol or of *p*-cresol (Böeseken, Metz, and Pluim, *Rec. Trav. chim.*, 1935, **54**, 345). The last is contrary to a statement by Karrer (*loc. cit.*), doubtless made because of the apparent discrepancy in melting point. We have shown (Elvidge, Linstead, and Sims, preceding paper) that this β-methylmuconic acid (m. p. ~170°) has the *cis-trans*-configuration.

Now it is clear from our work in the muconic series (*a*) that the *cis-cis*- and *cis-trans*-isomers may resemble each other closely and (*b*) that the inversion of the *cis-cis*-acid may be very easy. We therefore examined the ring-opening of the anhydride with considerable care. Ice-water and water vapour in the cold gave the same (*cis-trans*-) product as did boiling water. The *cis-trans*-acid (II) was also formed from the anhydride and cold aqueous sodium hydrogen carbonate, barium hydroxide, and dilute ammonia solution, so that the pH of the medium was evidently unimportant as regards the configuration of the product. It appears that the *cis-trans*-acid arises directly from the *cis-cis*-anhydride. In these and the subsequently described reactions, the precaution was taken of performing the operations as far as possible in the dark.

Esters and Amides derived from the Anhydride.—An attempt to open the ring of the anhydride (I) under neutral and anhydrous conditions, with dry methanol containing diazomethane, led only to a nitrogenous product. With cold dry methanol alone, a mixture of (α)-methyl (δ)-hydrogen and (δ)-methyl (α)-hydrogen β-methyl *cis-trans*-muconates, (III) and (IV), resulted, which was separated by fractional crystallisation. After a longer reaction time, the product was a mixture of the former half-ester (III) with Pauly and Will's lactonic ester (V). Thus the half-ester product (IV), with the free α-carboxyl group, rapidly underwent lactonisation (see preceding paper). The anhydride (I) was also treated with barium hydroxide in absolute methanol, and the precipitated barium salt decomposed with sulphuric acid in methanol. Following treatment with diazomethane, methyl β-methyl-*cis-trans*-muconate was isolated.

Karrer *et al.* (*loc. cit.*) reported that with dry ammonia in benzene, the anhydride gave a half-amide of β-methyl-*cis-cis*-muconic acid with m. p. 147—149° (decomp.). Since their method of isolation merely involved evaporation of the reaction mixture and crystallisation of the residue from ethanol–ether, it seemed unlikely that their product could have been an *acid*. Repetition of the experiment afforded a similar product (m. p.; solubility) which, however, was a mixture. The main constituent (extracted by ethanol) was the amide (VI), m. p. 148—149°, of Pauly and Will's lactone, presumably the product isolated by Karrer and his collaborators. The ethanol-insoluble fraction was evidently a mixture of ammonium salts, since after acidification the presence of both the acid amides of β-methyl-*cis-trans*-muconic acid, (VII) and (VIII), was demonstrated. Thus by treatment of the acidified mixture with diazomethane, and fractional crystallisation, β-methyl-*cis-trans*-muconic (α)-methyl ester (δ)-amide (IX) was obtained. On the other hand, by making use of the facts (preceding paper) that the (α)-acid (δ)-amide (VII) readily isomerises in boiling water to the lactonic amide (VI) whereas the positionally-isomeric (α)-amide (δ)-acid (VIII) is unaffected, isolation of the latter amide acid was achieved. Esterification gave the β-methyl-*cis-trans*-muconic (α)-amide (δ)-methyl ester (X), whilst from the aqueous filtrate the product of lactonisation of the acid amide (VII), *viz.* the lactonic amide (VI), was obtained.

* Incidentally the melting point and the four references which Karrer *et al.* give for β-methyl-*trans-trans*-muconic acid actually relate to muconic acid.

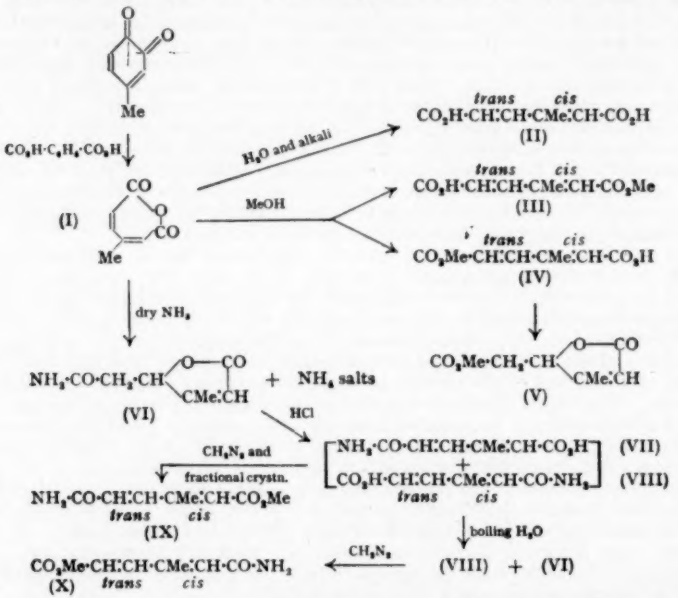
The immediate formation of the lactonic amide (VI) from the anhydride (I) and ammonia suggests that it arises directly and not through the intermediate formation of an amic acid.

The various experimental results are summarised in the scheme below.

In summary, therefore, only *cis-trans* products have been obtained from the *cis-cis*-anhydride (I), and we consider the claims of Karrer, Schwyzer, and Neuwirth to have isolated the *cis-cis*-isomer of β-methylmuconic acid and one of its half-amides to be in error. Karrer, Schwyzer, and Neuwirth (*loc. cit.*) wrote : " The existence of β-methyl-*cis-cis*-muconic acid has a connection of interest with the theory proposed by Pauling (*Fortschr.*, **1939**, **3**, 203) for carotenoid structure. This theory states that in carotenoid molecules only double bonds at carbons carrying methyl groups can have *cis*-configurations, except the central double bond; on the other hand a *cis*-configuration for the other double bonds is not possible on steric grounds." . . . " The existence and stability of β-methyl-*cis-cis*-muconic acid show that this theory can hardly be correct because here is encountered in an atomic environment identical with that in the carotenoids a $-CH{=}CH-$ group which shows no resistance to taking up a *cis*-configuration." In the light of our new experimental work this criticism loses its validity.

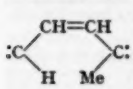
In a reply to Karrer, Pauling (*Helv. Chim. Acta*, **1949**, **32**, 2241) has reiterated his original concepts (that resonance can occur within conjugated systems, leading to enhanced stability, provided a planar configuration is possible), and he has re-stated his central conclusion that in a carotenoid molecule only certain of the double bonds will (therefore, for steric reasons) be capable of assuming a *cis*-configuration. He emphasises that the conclusion is more rigorously applicable to long conjugated systems than to short, and suggests that exceptions, especially in the latter case, could be expected. The immediate reason for expanding the original views is now seen to exist no longer.

The essential point is whether any of the geometrical forms of a diene or polyene can exist in an unhindered planar state and thus be *fully* conjugated. If there is a difference in this respect between the *cis*- and the *trans*-form about one double bond then the hindered form will have a much enhanced instability (or energy content) over its geometrical isomer and be either difficult or impossible to prepare. If, on the other hand, *both* geometrical forms are prevented



by hindrance from becoming planar the *difference* in energy content between them will be much less and we can conceive that both isomerides will be obtainable and that the *cis*-form may be relatively stable.

Scale models indicate that in β-methylmuconic acid, the *cis-trans*-isomer is unhindered, whereas the *cis-cis*-isomer would have a non-planar structure. Pauling has calculated a value of 7·1 kcal./mol. for the instability of the non-planar β-methyl *cis-cis*-muconic acid over the *trans-trans*-form, and a corresponding reduction in resonance stabilisation of more than twice this value for longer conjugated systems (*e.g.* carotenoid molecules) which are not fully coplanar because they possess the *cis*-configuration about one double bond of the type shown inset. It seems unlikely that such forms would ordinarily be obtainable.



In our view the ideas of Pauling and Zechmeister (Zeichmeister, *Chem. Reviews*, 1944, **34**, 267) concerning stereoisomerism in the carotenoids are strengthened by the known facts concerning the isomeric β-methylmuconic acids.

Experimental.

(M. p.s marked • were taken from a bath at 165° with the temperature rising at 8°/minute. Other m. p.s were determined normally.)

Authentic materials employed for the various mixed-m. p. comparisons have been described in the preceding paper).

β-Methylmuconic Anhydride.—To freshly prepared 4-methyl-1 : 2-benzoquinone (3·2 g.) [prepared in 32% yield by Willstätter and Müller's method (*Ber.*, 1911, **44**, 2171)] suspended in ice-cooled anhydrous ether (250 c.c.), crystalline monoperphthalic acid (13 g.; 51% of $CO_3H{\cdot}C_6H_4{\cdot}CO_2H$) was added slowly. The mixture was kept at room temperature overnight and then filtered, the filtrate evaporated under reduced pressure, and the residue treated with dry benzene (20 c.c.). Evaporation of the filtered benzene extract afforded a mixture of needles with a gum, which was extracted with boiling light petroleum (b. p. 60—80°) (6 × 100 c.c.). β-Methylmuconic anhydride (2·2 g., 61%) crystallised from the extract as needles, m. p. 72—73° raised to 73—74° on repeated crystallisation (4 times) from dry ether (Found : C, 61·15; H, 4·8. Calc. for $C_7H_8O_3$: C, 60·9; H, 4·4%). Karrer *et al.* (*loc. cit.*) give m. p. 75—76°, taken from a bath at 70°. Light absorption in dry dioxan : Max. at 2650 and 2800 Å; ε = 4970 and 4970.

Reactions of the Anhydride.—(a) *With water.* (i) The anhydride (0·2 g.) was treated with boiling water (2 c.c.) for 1 minute. The solution was cooled, and the product recrystallised from hot water yielding needles (0·13 g., 57%), m. p. 173—174° •, and m. p. 177—178° • when mixed with β-methyl-*cis-trans*-muconic acid. Treatment of the product with ethereal diazomethane afforded methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38·5°. (ii) The anhydride (0·2 g.) was kept with ice-cold water (2 c.c.) for 1 hour and the product recrystallised from ethanol giving micro-needles (0·15 g., 66%), m. p. 178—179° • not depressed by β-methyl-*cis-trans*-muconic acid. Treatment of the product with ethereal diazomethane gave methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38—38·5°.

(b) *With water vapour.* The finely powdered anhydride (0·1 g.) was spread on a watch glass and kept for 24 hours in a closed vessel containing a dish of water. Treatment of the product with ethereal diazomethane afforded only needles, m. p. 35—36°, and m. p. 36—37° when mixed with methyl β-methyl-*cis-trans*-muconate.

(c) *With aqueous alkali.* (i) The anhydride (0·2 g.) was stirred with saturated aqueous sodium hydrogen carbonate (2 c.c.), the solution cooled in ice and acidified (10% hydrochloric acid; Congo-red). The precipitate (0·13 g., 57%), collected at once and washed with cold water, had m. p. 178—179° • alone and when mixed with β-methyl-*cis-trans*-muconic acid. With diazomethane in ether the product gave methyl β-methyl-*cis-trans*-muconate (needles), m. p. 35—36° and mixed m. p. 35—38°. (ii) The anhydride (0·2 g.) was added to cold N-barium hydroxide (2 c.c.), and the solution then made acid (hydrochloric acid; Congo-red). Crystallisation of the precipitate from ethanol afforded β-methyl-*cis-trans*-muconic acid (0·15 g., 66%) as micro-needles, m. p. and mixed m. p. 177—178° •. With ethereal diazomethane, methyl β-methyl-*cis-trans*-muconate was obtained, m. p. and mixed m. p. 38°. (iii) The anhydride (0·1 g.) was dissolved in 2N-aqueous ammonia (2 c.c.), and the solution cooled in ice and acidified. β-Methyl-*cis-trans*-muconic acid was obtained as micro-needles (from ethanol), m. p. and mixed m. p. 177—178° •. Treatment of the crude product with ethereal diazomethane gave methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 37—38°.

(d) *With methanol.* (i) The anhydride (0·5 g.) was dissolved in anhydrous methanol (5 c.c.), the solution evaporated under reduced pressure, and the residue fractionally crystallised from dry benzene, yielding two crystal crops. The least-soluble fraction (0·25 g., 40%) had m. p. 168—169°, undepressed by (α)-methyl (δ)-hydrogen β-methyl-*cis-trans*-muconate † (m. p. 170°), and afforded with ethereal diazomethane methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38°. The more-soluble fraction (0·2 g., 32%) had m. p. 125—126°, alone and in admixture with (δ)-methyl (α)-hydrogen β-methyl-*cis-trans*-muconate,† and reacted with ethereal diazomethane to yield methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38°. (ii) The anhydride (2·5 g.) was kept with anhydrous methanol (20 c.c.) for 48 hours in the dark, and the solution then allowed to evaporate spontaneously. A mixture of an oil and needles was obtained. This solid (1·4 g., 45%) had m. p. 168—169°, undepressed by (α)-methyl (δ)-hydrogen β-methyl-*cis-trans*-muconate. The oil was taken up in ether (50 c.c.), the solution washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated under reduced pressure, and the residue distilled to give γ-carbomethoxymethyl-β-methyl-Δ^{α}-butenolide (0·42 g., 14%), b. p. 179°/11 mm., which soon crystallised as needles, m. p. 34—35° undepressed by authentic material.

† For nomenclature see Elvidge, Linstead, and Sims, preceding paper.

(e) *With methanolic barium hydroxide.* The anhydride (0·5 g.) was treated with anhydrous methanolic barium hydroxide (5 c.c; 1N). The precipitate was suspended in fresh anhydrous methanol (100 c.c.) and a 1% solution of sulphuric acid in anhydrous methanol (35 c.c.) added. The filtrate was evaporated under reduced pressure and the residue treated with diazomethane in ether to yield methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38·5°.

(f) *With dry ammonia.* (i) A stream of dry ammonia was passed for 3 minutes into a solution of the anhydride (0·15 g.) in anhydrous benzene (5 c.c.). The benzene was evaporated under reduced pressure and the deliquescent residue extracted with boiling absolute ethanol (5 c.c.). The extract was filtered from insoluble material, concentrated under reduced pressure to a small bulk, cooled in ice, and treated dropwise with dry ether. The amide of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide crystallised (40 mg., 25%) as needles, m. p. and mixed m. p. 148—149°. (ii) Dry ammonia was passed for 3 minutes into an ice-cooled solution of the anhydride (1 g.) in dry benzene (10 c.c.). The benzene was then evaporated under reduced pressure, the residue dissolved in water (3 c.c.), and the solution acidified (hydrochloric acid; Congo-red). A mixture (*A*), mainly of the acid amide (VII) and amide acid (VIII), was precipitated (650 mg., 58%), m. p 140—175°. The filtrate was evaporated, the residue extracted with ethanol (5 c.c.), and the solution concentrated. The amide of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (300 mg., 26%) crystallised; it had m. p. and mixed m. p. 149—150°. A portion of the mixture (*A*) (200 mg.) was treated with an excess of diazomethane in ether, and the product fractionally crystallised from methanol. β-Methyl-*cis-trans*-muconic (α)-methyl ester (δ)-amide (IX) (80 mg.) was obtained, m. p. and mixed m. p. 160—161°. A second portion of the mixture (*A*) (50 mg.) was heated with water (5 c.c.) under reflux for 3 hours and the solution cooled. β-Methyl-*cis-trans*-muconic (α)-amide (δ)-acid (VIII) (30 mg., 60%) crystallised [filtrate (*B*)], m. p. and mixed m. p. 210—211°, and reacted with diazomethane to yield β-methyl-*cis-trans*-muconic (α)-amide (δ)-methyl ester (X), m. p. and mixed m. p. 141°. The filtrate (*B*) from the amide acid (VIII) was evaporated to yield the amide of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (10 mg.), which after crystallisation from ethanol had m. p. and mixed m. p. 146—148°.

We are indebted to the Ministry of Education for a grant (to P. S.).

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[*Received, July 17th,* 1951.]

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748. *Mechanism of Decarbonylation. The Kinetics of the Decarbonylation of Benzoylformic Acid in Slightly Aqueous Sulphuric Acid.*

By W. W. ELLIOTT and D. LL. HAMMICK.

The decarbonylation of (loss of carbon monoxide from) benzoylformic acid in slightly aqueous sulphuric acid has been found to be a first-order process, and the variation of rate constant with temperature to be expressed by the equation $k = 9{\cdot}4 \times 10^{10} \cdot e^{-18,800/RT}$ sec.$^{-1}$. The rate of reaction is markedly inhibited by the addition of basic solutes, and the variation of reaction rate with the concentration of inhibitor may be accounted for by assuming that decarbonylation proceeds by unimolecular decomposition of the benzoylformic diacidium ion, $C_6H_5 \cdot C(^+OH) \cdot C(=O) \cdot OH$, and that this unstable ion is only formed to a limited extent in the solvent, sulphuric acid 98% plus water 2%.

THE decarbonylation reaction, *i.e.*, the degradative reaction whereby a carbonyl group is eliminated from an organic compound as carbon monoxide, occurs in a wide variety of types of carbonyl compound, *e.g.*, α-keto-acids, α-hydroxy-acids, formic and oxalic acids and their derivatives, aldehydes, ketones, and acids of the type $R_3C \cdot CO_2H$, where R may be an alkyl or an aryl group. The reaction occurs under a variety of conditions, *e.g.*, pyrolysis, proton-acid catalysis, Lewis-acid catalysis, base catalysis. There has been, however, relatively little work reported on the mechanism of the reaction. The kinetics of decarbonylation of formic acid (Schierz, *J. Amer. Chem. Soc.*, 1923, **45**, 447; De Right, *ibid.*, 1933, **55**, 4761), citric acid (Wiig, *ibid.*, 1930, **52**, 4729), oxalic acid (Lichty, *J. Phys. Chem.*, 1907, **11**, 225), malic acid (Whitford, *J. Amer. Chem. Soc.*, 1925, **47**, 953; Dittmar, *ibid.*, 1930, **52**, 2747), and triphenylacetic acid (Dittmar, *ibid.*, 1929, **51**, 533) have been studied in sulphuric acid solutions, but no satisfactory mechanism of reaction has been suggested by the above workers. Decarbonylation of ethyl pyruvate (Calvin and Lemmon, *ibid.*, 1947, **69**, 1232) and diphenylpropane-1 : 2 : 3-trione (dibenzoylformaldehyde) (Roberts, Smith, and Lee, *ibid.*, 1951, **73**, 618) has been studied

by using radioactive tracers. Calvin and Lemmon (*loc. cit.*) showed that, in the case of ethyl pyruvate, the carboxyl-carbon atom is eliminated as carbon monoxide.

We have investigated the decarbonylation of benzoylformic acid in slightly aqueous sulphuric acid: $Ph{\cdot}CO{\cdot}CO_2H \longrightarrow Ph{\cdot}CO_2H + CO$. This acid was chosen since (*a*) the decarbonylation had been reported to be quantitative (Bistrzycki and Siemiradzki, *Ber.*, 1906, **39**, 51), (*b*) there is little change in the acidity of the solution as the reaction proceeds, and (*c*) the acid contains no basic groups other than those requisite to the reaction and contains no labile hydrogen atoms.

Experimental.

The decarbonylation was followed kinetically by measuring the volume of carbon monoxide evolved at constant pressure. The apparatus is represented diagrammatically in Fig. 1. A known volume of mercury is let out of the gas burette into the flow-meter (*F*), and the time take to restore atmospheric pressure in the gas burette is indicated by the mercury in the manometer arm (*M*) making a contact which causes a bell to ring. A further volume of mercury is let out and the process repeated until the run is complete. By this simple means it is possible to follow a fast rate of gas evolution closely and accurately. This method is especially suitable for studying gas evolutions that take place rapidly at or near room temperature, where there is little or no variable temperature gradient in the apparatus.

Each experimental run was commenced by melting the benzoylformic acid in the reaction tube, supercooling it to room temperature, and adding the solvent. A mercury-sealed stirrer was then fitted and, after some 10 minutes' stirring to allow thermal equilibrium to be established, readings were commenced. Temperature control to within 0·02° was ensured by an electrically heated water-bath.

In certain cases the rate constant was determined from the rate of formation of benzoic acid. This was found by titration, the benzoic acid being removed from the reaction mixture by diluting a sample with water and extracting the acid with carbon disulphide.

Results.

That the reaction is a normal homogeneous reaction in solution has been demonstrated in two ways. First, the rate of evolution of carbon monoxide was found to be independent of the nature of the walls of the reaction vessel if the reaction mixture was stirred. Secondly, the rate of formation of benzoic acid in the absence of stirring is the same as the rate of evolution of gas when the reaction mixture is stirred.

The rate of evolution of carbon monoxide was found to be a first-order process with respect to benzoylformic acid. Details of a specimen kinetic run are given below, and the rate of gas evolution, volume against time, is plotted in Fig. 2.

Volume units	0	2	4	6	8	10	12	14	16	18
Time, sec.	0	18	38	61	84	112	140	170	204	240
Volume units	20	22	23	24	25	26	27	28	28·5	29
Time, sec.	284	336	368	406	448	491	544	606	650	693

Temperature 306·0° K. Solvent, 98% H_2SO_4 in large excess.

The rate constant was determined from Fig. 2 by Guggenheim's method (*Phil. Mag.*, 1926, **2**, 538). The log $(v' - v)$ terms are tabulated below and, from the plot against time, it is found that the slope $= 0{\cdot}434k = 0{\cdot}00151$; *i.e.*, $k = 0{\cdot}00344$ sec.$^{-1}$.

Time, sec.	0	40	80	120	160	200	240	280	320
v_T	0	4·20	7·60	10·60	13·40	15·85	18·05	19·85	21·35
v'_{T+380}	22·80	23·80	24·80	25·75	26·60	27·25	27·90	28·40	28·85
log $(v' - v)$	1·358	1·292	1·235	1·180	1·121	1·057	0·993	0·932	0·875

Though most of the rate constants were calculated by this method, a few runs were allowed to go to completion, and in such cases the rate constants calculated by the end-volume method agree with those calculated by Guggenheim's method.

The rate constants observed at various temperatures are tabulated below. The variation of rate constant with temperature may be expressed by the equation

$$k = 9{\cdot}4 \times 10^{10} \cdot e^{-13{,}800/RT} \text{ sec.}^{-1}$$

Temp., ° K.	291·3	297·9	302·3	306·0
10^4k, mean, obs.	7·14	14·6	25·0	34·3
10^4k, calc.	7·25	14·8	23·5	34·7

These results were obtained with a mixture containing 98% (by weight) sulphuric acid and 2% water as solvent, which was in large excess over the solute, benzoylformic acid. This concentration of sulphuric acid was used so that the concentration of bisulphate ions present in the excess of solvent should be large compared with that of bisulphate ions arising from the ionisation of the benzoylformic acid according to the equilibrium

$$Ph{\cdot}CO{\cdot}CO_2H + H_2SO_4 \rightleftharpoons (Ph{\cdot}CO{\cdot}CO_2H{\cdot}H)^+ + HSO_4^-$$

FIG. 1.

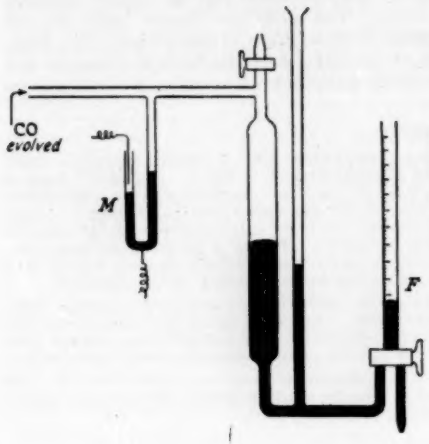


FIG. 2.

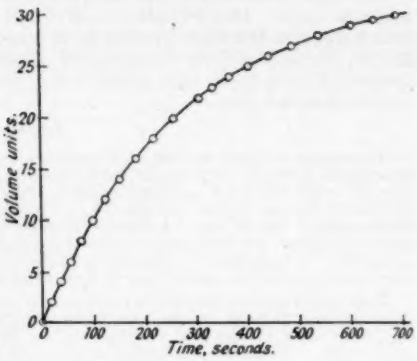
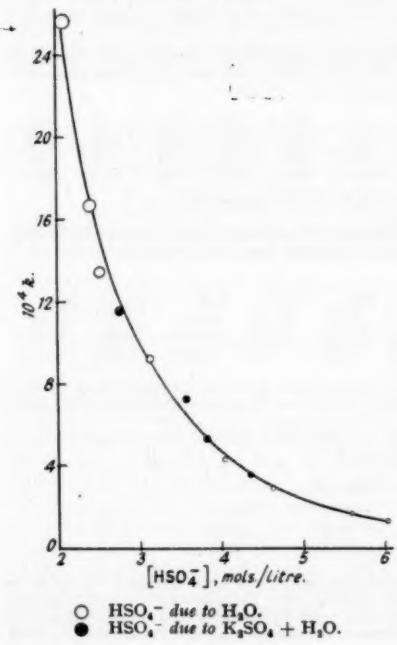
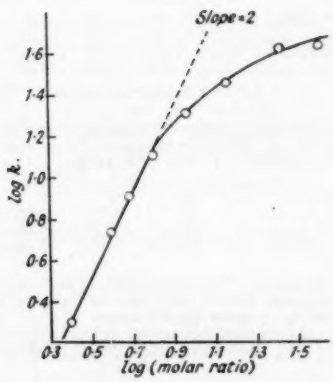


FIG. 3.



○ HSO_4^- *due to* H_2O.
● HSO_4^- *due to* $K_2SO_4 + H_2O$.

FIG. 4.



The variation of reaction rate by the addition of the solutes water and potassium sulphate was determined by making up solvents of various composition by direct weighing. Details are tabulated below and the rate constants are plotted against bisulphate-ion concentrations in Fig. 3.

Comptn. of solvent, % by wt.:			Molarities of solvent: Undiss.		10^4k,	Comptn. of solvent, % by wt.:			Molarities of solvent: Undiss.		10^4k,
H_2SO_4	H_2O	K_2SO_4	H_2SO_4	HSO_4^-	sec.$^{-1}$	H_2SO_4	H_2O	K_2SO_4	H_2SO_4	HSO_4^-	sec.$^{-1}$
98·00	2·00	nil	16·24	2·03	25·0	94·43	5·57	—	11·97	5·64	1·77
97·63	2·37	—	15·80	2·40	16·7	94·05	5·95	—	11·49	6·02	1·37
97·53	2·47	—	15·67	2·51	13·5	94·40	1·93	3·67	16·23	2·75	11·6
96·92	3·08	—	14·95	3·13	9·27	90·39	1·84	7·77	14·85	3·58	7·39
96·03	3·97	—	13·87	4·03	4·35	89·26	1·82	8·92	14·34	3·82	5·36
95·43	4·57	—	13·15	4·63	2·95	86·81	1·77	11·42	13·79	4·36	3·69

The molarities of undissociated sulphuric acid and of bisulphate ions have been calculated by assuming that the basic solutes react according to the equations:

$$H_2O + H_2SO_4 = H_3O^+ + HSO_4^-$$

$$K_2SO_4 + H_2SO_4 = 2K^+ + 2HSO_4^-$$

In order to determine the molarities recorded above, the densities of the H_2SO_4–H_2O–K_2SO_4 mixtures were determined by the relative density method. The densities determined at 18° were corrected to the reaction temperature (29·1°) and are recorded below.

Comptn. of solvent, % by wt.			
H_2SO_4	H_2O	K_2SO_4	Relative density
98·00	2·00	—	1·827
95·07	1·94	2·99	1·848
90·70	1·85	7·45	1·880
86·36	1·76	11·88	1·912

From Fig. 3 it can be seen that the inhibition produced by the addition of the basic solutes is dependent on the concentration of the bisulphate ions produced by the basic solute; *e.g.*, the addition of 2 g.-mol./l. of water produces the same effect as the addition of 1 g.-mol./l. of potassium sulphate.

In order to indicate the order of the catalytic effect of the solvent, the rate of decarbonylation was determined under conditions where the solvent, 98% sulphuric acid, was not in large excess. This procedure virtually dilutes the solvent. An inert solvent cannot be employed as diluent since aprotic solvents are immiscible with sulphuric acid, and basic solvents, *e.g.*, nitrobenzene, inhibit the reaction. The observed rate constants and molar ratios of sulphuric acid to benzoylformic acid are tabulated below, and in Fig. 4 log (rate constant) is plotted against log (molar ratio).

Molar ratio	2·56	3·88	4·83	6·29	9·30	14·6	25·9	40·8
10^5k, sec.$^{-1}$	1·93	5·50	8·10	12·8	20·7	28·4	41·6	40·6

The decarbonylation of formic acid at 18·15° in 98% sulphuric acid was investigated and the rate constant found to be $42·8 \times 10^{-4}$ sec.$^{-1}$. Under the same conditions the rate of decarbonylation of benzoylformic acid is $7·1 \times 10^{-4}$ sec.$^{-1}$. Therefore the decomposition of benzoylformic is unlikely to involve a fast preliminary solvolysis followed by decarbonylation of formic acid. This conclusion is supported by the fact that the rate of formation of benzoic acid is equal to the rate of evolution of carbon monoxide.

Ethyl benzoylformate is not decarbonylated under conditions similar to those employed in the kinetic experiments upon benzoylformic acid. Gas evolution, however, commences at *ca.* 60° and benzoic acid is produced. It is thought likely that the ester is decarbonylated by means of a preliminary hydrolysis to benzoylformic acid, since both ethyl benzoylformate and ethyl benzoate are reasonably stable in 98% sulphuric acid at room temperature, but benzoic acid is produced in both cases when the esters are heated to 80° for some ten minutes.

Discussion.

The marked inhibition produced by the addition of bases indicates that some acidic or positive species essential to the reaction mechanism is destroyed by the basic solute or by the basic product of the basic solute, namely, the bisulphate ion. The positively charged species likely to be present in a solution of benzoylformic acid in slightly aqueous sulphuric acid are the benzoylformic mono- and di-acidium ions, the ions derived from the autoprotolysis of the solvent, and hydroxonium ions. In order to ascertain the active species, the logarithm of the rate constant was plotted against Hammett and Deyrup's values for the acidity function H_0 (*J. Amer. Chem. Soc.*, 1932, **54**, 2721). The slope of the plot was −2·1, indicating that the reactive species may be the benzoylformic diacidium ion, *i.e.*, the product of the transfer of two protons from the solvent to the neutral substrate. In this connection it may be pointed out that both benzoic acid and acetone are strong bases in sulphuric acid (Gillespie, *J.*, 1950, 2473). If this conclusion is valid, it requires that the acidity function H_0 should vary

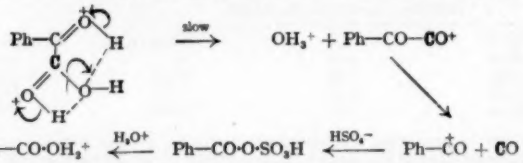
approximately as the acidity function H_+ over the investigated range of acidities, *i.e.*, $\Delta H_0 \simeq \Delta H_+$, where H_+ is the acidity function for a unit positively charged conjugate base. This would require that the function $f_{BH^{++}}/f_B \cdot f_{BH_2}{}^{++}$ is approximately constant over the determined range of acidities. The same conclusion may be reached without recourse to Hammett's acidity function. Thus

$$HA + 2H_2SO_4 \rightleftharpoons H_2A^{++} + 2HSO_4^-$$

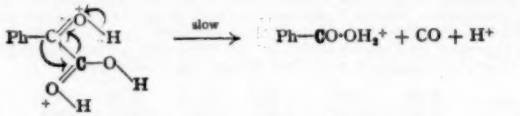
i.e.,
$$[H_2A^{++}] = K_c[HA][H_2SO_4]^2/[HSO_4^-]^2$$

If the reaction rate is proportional to the concentration of the active species H_2A^{++}, then $[H_2SO_4]^2/[HSO_4^-]^2$ is proportional to the rate constant. The curve drawn in Fig. 3 is a plot of the function, constant $\times$ $[H_2SO_4]^2/[HSO_4^-]^2$, and the excellent agreement obtained between this theoretically derived curve and the experimentally determined points indicates that the relation is obeyed. If this conclusion is valid it means that the activity coefficients may be ignored in the determined range of solvent concentrations. Gillespie (*loc. cit.*) has stated that interionic forces in sulphuric acid appear to be unusually low and that the cryoscopic constant may be calculated from the depression of freezing point produced by ionic solutes. Hammett and Lowenheim (*J. Amer. Chem. Soc.*, 1934, **56**, 2620) have also found that ionic solutes appear to behave ideally up to ionic strengths of at least 2.

There appear to be two possible modes of decomposition of the benzoylformic diacidium ion : (*A*) An interionic mechanism involving the loss of the carboxyl carbon atom as carbon monoxide :



(*B*) An intramolecular rearrangement with the loss of the carbonyl carbon atom as carbon monoxide :



Mechanism (*A*) appears to be the more probable; for, first, Calvin and Lemmon (*loc. cit.*) have shown that the carboxyl carbon atom is lost in the pyrolytic decarbonylation of ethyl pyruvate, and secondly, there appears to be some evidence for the finite existence of an intermediate carbonium ion in other decarbonylation reactions, *e.g.*, triphenylacetic acid (Dittmar, *loc. cit.*) :

$$Ph_3C·CO_2H + 2H_2SO_4 = Ph_3C^+ + H_3O^+ + CO + 2HSO_4^-$$

and the aluminium chloride-catalysed decarbonylation of dichloroacetyl chloride (Boeseken, *Proc. K. Akad. Wetensch. Amsterdam*, 1909, **12**, 417) :

$$CHCl_2·CO·Cl + AlCl_3 = CHCl_2·CO^+ + AlCl_4^- = CHCl_3 + CO + AlCl_3$$

We have applied the foregoing methods to the experimental results of earlier workers, *i.e.*, plotting log (rate constant) against H_0 and also against log $[H_2SO_4]/[HSO_4^-]$, and the slopes thus found are tabulated below. Hammett (*Chem. Reviews*, 1935, **16**, 67) has also plotted log (rate constant) against H_0 and found approximately similar slopes to those here recorded, for formic, malic, citric, and triphenylacetic acids.

Acid	Solvent range : H_2SO_4, %	H_0 plot	$\log \frac{[H_2SO_4]}{[HSO_4^-]}$ plot
Formic (De Right)	96 —98·5	1·2	1·2
Malic (Whitford)	96·5—99·2	*ca.* 0·9	1·1
Oxalic (Lichty)	90 —96	*ca.* 1·2	1·1
	98 —100	2·0	—
Citric (Wiig)	95 —98·8	*ca.* 2·0	2·1
Benzoylformic (present authors)	94 —98	2·1	2·0
Triphenylacetic (Dittmar)	93 —97	2·6	2·3

It would therefore appear that formic and malic acids decompose through their monoacidium ions and that citric and benzoylformic acids decompose through their diacidium ions in the solvent ranges indicated; also that oxalic acid may decompose through both types of ion, the di-acidium ion only existing in significant concentration in the solvent range 97—100% H_2SO_4. Triphenylacetic acid appears to be anomalous in two respects: first, it is the only case where the slopes are not approximately integral, and secondly, it is the only case where the number of protons taken up is apparently greater than the number of basic centres in the molecule. This would suggest that triphenylacetic acid decomposes by a different mechanism, perhaps by conversion into a monoacidium ion which interacts with the solvent without proton transfer, *e.g.*, a pseudo-unimolecular dehydration:

$$Ph_3C{\cdot}CO_2H_4^+ + H_2SO_4 \xrightarrow{\text{slow}} PhC^+ + CO + H_3O^+ + HSO_4^-$$

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749. *The Mechanism of the Decarboxylation of Substituted Malonic Acid Derivatives.*

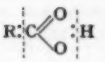
By J. KENYON and W. A. ROSS.

Experiments have been carried out on the decarboxylation of optically active disubstituted malonic acid derivatives. The results are consistent with the special intramolecular decarboxylation mechanism proposed by Westheimer and Jones (*J. Amer. Chem. Soc.*, 1941, **63**, 3283) and Schenkel and Schenkel-Rudin (*Helv. Chim. Acta*, 1948, **31**, 514) for the decarboxylation of β-keto-acids.

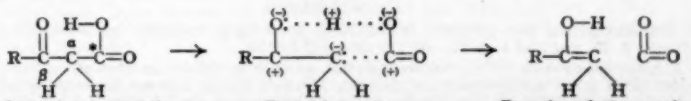
The preparation and the decarboxylation of optically active ethyl hydrogen ethylmethylmalonate, ethylmethylcyanoacetic acid, and α-benzyl-α-cyanopropionic acid, to give optically inactive decarboxylation products, are described. The preparation of the products of decarboxylation in optically active forms, and their optical stability to heat, are also described.

KINETIC measurements of the decarboxylation of malonic acid and its mono- and di-substituted derivatives, under a wide variety of experimental conditions, have been made by several workers (*inter al.*, Lindner, *Monatsh.*, 1907, **28**, 1041; Bernouilli and Wege, *Helv. Chim. Acta*, 1919, **2**, 511; Bernouilli and Jakubowicz, *ibid.*, 1921, **4**, 1081; Hinshelwood, *J.*, 1920, **156**; Muus, *J. Phys. Chem.*, 1935, **39**, 343; Fairclough, *J.*, 1938, 1190; Ogata and Oda, *Bull. Inst. Phys. Chem. Res. Japan*, 1944, **23**, 217; Hall, *J. Amer. Chem. Soc.*, 1949, **71**, 2691). In almost all the experiments, the decarboxylation reactions were found to follow a first-order decomposition law.

A theory on the mechanism of decarboxylation reactions has been surveyed by Schenkel and Schenkel-Rudin (*Helv. Chim. Acta*, 1948, **31**, 514), who conclude that the decarboxylation of a carboxylic acid $R{\cdot}CO_2H$ in the liquid phase results in the retention of the binding electrons by R, which then combines with a liberated proton, the reaction being an electrophilic substitution (see inset).



The ready decarboxylation of β-keto-acids was explained by a special mechanism involving the formation of a double bond between C_α and C_β, the C_α–$^*C$ linkage dissociating unimolecularly. Thus the acid $R{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$ would be decarboxylated according to the following mechanism:



Configuration for reaction — Transition state — Decarboxylation product

. . . Bonds breaking or forming; : Position of electron pairs after fission.

It was suggested by Schenkel and Schenkel-Rudin that the decarboxylation of certain substituted malonic acids probably occurred by an analogous mechanism.

It was considered of interest to attempt to ascertain what contribution for or against such a mechanism could be made by studying the decarboxylation of optically active acids in which the molecular dissymmetry resided in the carbon atom α to the carboxyl group. If during the course of the reaction, a double bond were to be formed between C_α and C_β, then the molecular dissymmetry would be lost and the decarboxylation product would inevitably be racemic.

Accordingly, (±)-ethyl hydrogen ethylmethylmalonate was prepared from ethyl malonate and resolved into its optically active forms by the use of quinine and cinchonidine. When the (+)- and the (−)-ethyl hydrogen ethylmethylmalonates were decarboxylated at 170°, the resulting ethyl ethylmethylacetate was optically inactive. Since the lowest temperature at which decarboxylation occurred at a reasonable rate was 170°, it was considered desirable to examine the thermal stability of optically active ethyl ethylmethylacetate. The results recorded in the Experimental section show that this ester can be maintained at 175° for several hours, without suffering any loss in rotatory power.

The general similarity in chemical behaviour, and the comparable ease of decarboxylation by heat, of cyanoacetic acid formed the basis of a second series of experiments in which decarboxylation experiments were carried out with optically active disubstituted cyanoacetic acids. (±)-Ethylmethylcyanoacetic acid [(±)-α-cyano-α-methylbutyric acid] was prepared from ethyl cyanoacetate, but it was not found possible to resolve it into its optically active forms by the use of its crystalline salts with brucine, quinine, cinchonidine, or quinidine. No ready explanation can be advanced for this failure, since other disubstituted cyanoacetic acids have been resolved without notable difficulty (*e.g.*, Fischer and Flatau, *Ber.*, 1909, **42**, 2981). An active ethylmethylcyanoacetic acid was obtained by the use of strychnine although recrystallisation of this alkaloidal salt proved very difficult and, as a result, the acid obtained was probably not optically pure.

(+)-Ethylmethylcyanoacetic acid underwent decarboxylation at 180—190° and the resulting ethylmethylacetonitrile (α-methylbutyronitrile) proved inactive. In this case also experiments were made to examine the thermal stability of the decarboxylation product. Ethylmethylacetonitrile was obtained in an optically active form by the interaction of phosphoric oxide with (−)-ethylmethylacetamide, itself obtained from (±)-ethylmethylacetic acid, which was resolved by the method of Schütz and Marckwald (*Ber.*, 1896, **29**, 53). It was found that (−)-ethylmethylacetonitrile could be kept at 175° for several hours without loss of rotatory power.

By converting the (−)-ethylmethylacetonitrile into (−)-ethylmethylacetic acid by hydrolysis and by comparison of the rotatory powers of the (−)-ethylmethylacetic acid obtained with that of the acid used in the preparation of the (−)-nitrile, an approximate value for the specific rotation of the nitrile could be calculated.

Decarboxylation experiments were then repeated using another disubstituted cyanoacetic acid. (±)-α-Benzyl-α-cyanopropionic acid was prepared from ethyl cyanoacetate, and resolved into its optically active forms by the use of brucine. (+)- and (−)-α-Benzyl-α-cyanopropionic acids underwent smooth decarboxylation at 165°/18 mm., to yield α-benzylpropionitrile which also was devoid of optical activity.

The decarboxylation product was obtained in an optically active form by the interaction of phosphoric oxide with (+)-α-benzylpropionamide, itself prepared from (±)-α-benzylpropionic acid, which was resolved by the method of Kipping and Hunter (*J.*, 1903, 1005). It was found that (+)-α-benzylpropionitrile could be kept at 160—170° for several hours, without loss of rotatory power. By hydrolysing (+)-α-benzylpropionitrile to (+)-α-benzylpropionic acid, an approximate value for the specific rotation of the nitrile was calculated.

The close resemblance between these decarboxylation experiments and the Marckwald asymmetric synthesis (*Ber.*, 1904, **37**, 349) led to a reinvestigation of this experiment, the results of which will be communicated shortly.

Experimental.

Ethyl methylmalonate was prepared (yield, 75%) from ethyl malonate by the method described in *Org. Synth.*, **2**, 28, and had b. p. 93—95°/19 mm., n_D^{18} 1·4138.

Ethyl Ethylmethylmalonate.—To a stirred solution of sodium (32 g.) in absolute ethanol (600 c.c.) was slowly added ethyl methylmalonate (240 g.), followed during 3 hours by ethyl iodide (300 g.). The reaction was completed by heating the mixture under reflux for 0·5 hour. After removal of the precipitated sodium iodide by filtration, and of the ethanol by distillation, the residue was dissolved in ether, and the solution washed with water in which the separated sodium iodide had been dissolved. The aqueous layer was extracted three times with ether, the combined ethereal extracts were dried (Na_2SO_4), and the solvent was evaporated. The residual ester (83%) had b. p. 98—100°/15 mm., n_D^{18} 1·4190.

(±)-*Ethyl Hydrogen Ethylmethylmalonate.*—This was prepared by a method based on the procedure of Breslow, Baumgarten, and Hauser (*J. Amer. Chem. Soc.*, 1944, **66**, 1287); a preliminary experiment on unsubstituted ethyl malonate was carried out in order to ascertain the working conditions.

To a solution of ethyl ethylmethylmalonate (200 g.) in absolute ethanol (800 c.c.) was added during one hour, a solution of potassium hydroxide (60 g.) in absolute ethanol (700 c.c.). Next morning the solution was boiled and the crystals (A; 50 g.) insoluble in hot ethanol were removed by filtration. The filtrate was concentrated to 300 c.c. and cooled in ice, whereupon crystals (B; 120 g.) were obtained. Concentration of the second filtrate yielded a further small crop of crystals, which were added to B. Crop B was washed with dry ether and dried *in vacuo* over phosphoric oxide (Found: A, K, 46·0; B, K, 19·1. $C_8H_{14}O_4K_2$ requires K, 35·1. $C_8H_{13}O_4K$ requires K, 18·4%). Thus, crop B (highly deliquescent needles) consisted largely of the potassium salt of the monoester. The yield was 51%, there being recovered unchanged diethyl ester (30 g.) and also the dipotassium salt (50 g.).

Concentrated hydrochloric acid (50 c.c.) was slowly added to a cold solution of the monopotassium salt (120 g.) in water (55 c.c.), and the resultant mixture extracted four times with ether. Evaporation of the dried (Na_2SO_4) ethereal solution yielded (±)-*ethyl hydrogen ethylmethylmalonate* which, after several hours *in vacuo* over sodium hydroxide, was obtained as a mobile, odourless liquid (96%) (on titration, 0·394 g. required 22·9 ml. of 0·1N-NaOH. $C_8H_{14}O_4$ requires 22·2 ml.). The S-*benzylthiuronium* salt, prepared in the usual way, was obtained as plate-like crystals (from aqueous ethanol), m. p. 117—118° (Found: N, 8·2; S, 9·3. $C_{16}H_{24}O_4N_2S$ requires N, 8·2; S, 9·4%).

Resolution. Quinine (72·5 g.) was added to a solution of (±)-ethyl hydrogen ethylmethylmalonate (38·5 g.) in aqueous ethanol (400 c.c. of 80%), and the whole warmed until dissolution was complete. After 2 days at 0°, the separated crystals were removed by filtration (43 g.; m. p. 103—110°). Two further recrystallisations from the same solvent gave a quinine salt (33 g.) as needles, m. p. 98—100°, which on decomposition with hydrochloric acid yielded (+)-*ethyl hydrogen ethylmethylmalonate* of constant rotatory power, $[\alpha]_D^{18}$ +3·38° (*l*, 2; *c*, 15·0 in chloroform).

A lævorotatory acid (22 g.) was obtained by decomposition of the more soluble fractions of the quinine salt. A portion of this acid (4 g.) was dissolved in acetone (30 c.c.), cinchonidine (6·8 g.) added, and the whole warmed until dissolution was complete. Three recrystallisations of the salt obtained from minimum quantities of acetone gave needles (5·6 g.) of m. p. 154—155°. The remainder of the acid (18 g.) was dissolved in acetone (250 c.c.), and cinchonidine (37·5 g.) was added. The solution was seeded with the recrystallised cinchonidine salt obtained earlier. Two recrystallisations from acetone gave needles (22 g.) of m. p. 155—156°, which on decomposition yielded the (−)-*ester* of $[\alpha]_D^{18}$ −3·47° (*l*, 2; *c*, 5·03 in chloroform); in one equivalent of aqueous sodium hydroxide, $[\alpha]_D^{18}$ was +3·64° (*l*, 2; *c*, 3·57).

Decarboxylation of (+)- *and* (−)-*Ethyl Hydrogen Ethylmethylmalonates.*—(i) The acid (2·0 g.) of $[\alpha]_D^{18}$ +3·38°, contained in a small distillation flask, was heated (oil-bath) at 170—175° for 2 hours. The distillate, dissolved in ether, was washed with dilute sodium hydrogen carbonate solution and dried (Na_2SO_4), and the solvent removed. The residual ethyl ethylmethylacetate (α-methylbutyrate) (1·22 g.) was devoid of optical activity in ethereal solution (*l*, 2; *c*, 3·35) and in the homogeneous state (*l*, 0·5).

(ii) The experiment was repeated with the acid (2·5 g.) of $[\alpha]_D^{25}$ −3·47°; the decarboxylation product was again optically inactive both in the homogeneous state (*l*, 0·5) and in ethereal solution (*l*, 2; *c*, 5·28).

Both distillates showed n_D^{20} 1·3965, and a mixture of the two was converted *via* the acid chloride into (±)-ethylmethylacetamide (α-methylbutyramide), which separated from ether in platelets, m. p. 108·5—109·5°, alone and when mixed with an authentic specimen.

Thermal Stability of Ethyl (−)-*Ethylmethylacetate.*—(±)-Ethylmethylacetic (α-methylbutyric) acid was prepared (yield, 93%) from ethyl ethylmethylmalonate, and resolved by Schütz and Marckwald's method (*Ber.*, 1896, **29**, 53). Three recrystallisations of the brucine salt gave the (−)-acid, b. p. 86·5—87·5°/26 mm., $[\alpha]_D^{20}$ −17·5° (homogeneous, d_4^{20} 0·934; *l*, 1). To the (−)-acid (5·5 g.) was added thionyl chloride (7 c.c.), and the mixture warmed on the steam-bath for 1 hour. The excess of thionyl chloride was removed and the (−)-acid chloride distilled (b. p. 115—120°; 5·2 g.). Treatment with absolute ethanol yielded ethyl (−)-ethylmethylacetate (5·2 g., 74%), b. p. 139—141°, $[\alpha]_D^{22}$ −17·5° (homogeneous, d_4^{22} 0·864; *l*, 0·5).

A specimen of the (−)-ester (1·0 g.), sealed in a glass tube, was heated (oil-bath) at 175° for 3 hours. The product showed b. p. 139—141°, $[\alpha]_D^{22}$ −17·5° (homogeneous, d_4^{22} 0·864; *l*, 0·5), before and after redistillation.

Ethyl (±)-*Ethylmethylcyanoacetate.*—This was prepared (56%) from ethyl cyanoacetate in an analogous manner and had b. p. 98—100°/19·5 mm., n_D^{19} 1·5725.

(±)-*Ethylmethylcyanoacetic* (α-*Cyano*-α-*methylbutyric*) *Acid.*—Hydrolysis of the ester by Henle and Haakh's method (*Ber.*, 1908, **41**, 4261) gave the acid as a pale yellow, hygroscopic oil (93%). Its *silver* salt forms needles, m. p. 155·5—156·5° (Found: Ag, 46·1. $C_6H_8O_2NAg$ requires Ag, 46·1%). The p-*bromophenacyl* ester, prepared from the acid in the usual way, separates from aqueous ethanol in platelets, m. p. 51·5—52·5° (Found: C, 51·9; H, 4·5; N, 4·1; Br, 24·5. $C_{14}H_{14}O_3NBr$ requires C, 51·9; H, 4·4; N, 4·3; Br, 24·6%).

Resolution. (i) After three recrystallisations, the brucine salt of the acid, prepared in the usual way, formed large prisms, m. p. 114—116°, from which only the (±)-acid could be obtained. (ii) A similarly recrystallised quinine salt (prisms) of m. p. 189—190° gave the (±)-acid on decomposition. (iii) The cinchonidine salt (needles) of m. p. 203—205° also afforded no resolution. (iv) No crystalline salt could be obtained with quinidine. (v) To the (±)-acid (4 g.) dissolved in aqueous ethanol (30 c.c. of 50%) was added strychnine (10·5 g.), and the whole warmed until dissolution was complete. After several weeks at room temperature, crystals (2·8 g.) of ill-defined crystalline form, m. p. 120—127°, were obtained.

To the (±)-acid (31 g.) in acetone (100 c.c.) was added strychnine (81·5 g.). The solution was concentrated to about half its volume, and seeded with the strychnine salt obtained earlier. After several weeks, when the solvent had almost completely evaporated, the needle-like crystals (15 g.) of m. p. 127—130° were removed from the viscous mother-liquor by decantation and quickly washed with small quantities of acetone. This salt was twice recrystallised from minimum quantities of acetone. Decomposition with dilute ammonia gave (+)-*ethylmethylcyanoacetic* (*α-cyano-α-methylbutyric*) *acid*, $[\alpha]_D^{20}$ +3·85° (*l*, 2; *c*, 5·99 in ethanol) (Found: equiv., 130·3. $C_6H_9O_2N$ requires equiv., 127·1).

Decarboxylation of (+)-*ethylmethylcyanoacetic acid*. The (+)-acid (2 g.) was decarboxylated under conditions similar to those used for (+)-ethyl hydrogen ethylmethylmalonate, the temperature being kept at 180—190°. The isolated ethylmethylacetonitrile (α-methylbutyronitrile), after purification (1·1 g.), was devoid of optical activity in the homogeneous state (*l*, 0·5) and in ethereal solution (*l*, 2; *c*, 5·3); it had n_D^{25} 1·3880, micro-b. p. 123°.

Thermal Stability of (−)-*Ethylmethylacetonitrile* (*α-Methylbutyronitrile*).—(−)-Ethylmethylacetyl chloride (37 g.) from partly resolved (−)-ethylmethylacetic acid was added during an hour to ammonia solution (80 c.c.; *d* 0·88) cooled in an ice-bath, and the mixture stirred continuously. The product was stirred for an additional half hour, and then evaporated to dryness *in vacuo* over concentrated sulphuric acid. The product was extracted for 3 hours in a Soxhlet apparatus with chloroform, to separate it from ammonium chloride. The chloroform solution was concentrated to 50 c.c. and ligroin added. The white, plate-like crystals obtained (19·2 g.) were recrystallised from chloroform–ligroin, (−)-ethylmethylacetamide (17·6 g., 62%), m. p. 113—114°, $[\alpha]_D^{24\cdot5}$ −4·21° (*l*, 2; *c*, 8·93 in water), being obtained.

To finely powdered (−)-ethylmethylacetamide (16·5 g.), in a 250-c.c. distillation flask, was added phosphoric oxide (28 g.), and the mixture quickly shaken to ensure thorough mixing. The mixture was heated over a flame, whereupon crude (−)-ethylmethylacetonitrile [(−)-α-methylbutyronitrile] (12 g.) distilled. The product was added to an equal volume of water, and anhydrous potassium carbonate added until the solution was saturated. The nitrile was separated and redistilled over phosphoric oxide (2 g.). The product (9·8 g., 72%), a colourless, volatile liquid, had b. p. 124·5—125·5°, n_D^{25} 1·3880, $[\alpha]_D^{25}$ −5·14° (homogeneous; d_4^{25} 0·824; *l*, 0·5).

The nitrile (2 g.), when heated (oil-bath) at 175° for 3 hours, showed $[\alpha]_D^{25}$ −5·14° (homogeneous, d_4^{25} 0·824; *l*, 0·5) and n_D^{25} 1·3880.

A portion of the (−)-nitrile (5·0 g.) was heated under reflux for 3 hours with concentrated hydrochloric acid (25 c.c.). It gave unchanged nitrile (2·4 g.) and (−)-ethylmethylacetic acid (2·6 g.), which after redistillation showed $[\alpha]_D^{20}$ −2·60° (homogeneous, d_4^{20} 0·934; *l*, 0·5). Thus the specific rotation of (−)-ethylmethylacetonitrile is between −22° and −33°. (The more probable value is −22°, since it was found, in the case of α-benzylpropionitrile, that considerable racemisation can occur during the hydrolysis of the optically active nitrile to the acid.)

Ethyl (±)-*α-Benzyl-α-cyanopropionate*.—The *ester*, prepared (37%) from ethyl cyanoacetate in the usual way, by substitution with methyl bromide and benzyl chloride, had n_D^{20} 1·498, b. p. 162—165°/14 mm. (Found: C, 71·6; H, 7·4; N, 6·4. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 7·0; N, 6·4%).

(±)-*α-Benzyl-α-cyanopropionic Acid*.—The ester (60 g.), mixed with alcoholic potasium hydroxide (290 c.c.; N.), was heated under reflux for 1·5 hours, and most of the alcohol removed by evaporation. The product (about 80 c.c.) was mixed with an equal volume of water, extracted three times with ether, acidified with hydrochloric acid, and again extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract yielded a product (48 g.) which slowly set to a solid (92%) of m. p. 73—79°. Recrystallisation from ligroin gave white leaflets of (±)-*α-benzyl-α-cyanopropionic acid*, m. p. 93—94° (Found: C, 69·8; H, 5·9; N, 7·4. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·9; N, 7·2%).

Resolution. Brucine (3·4 g.) was added to a solution of the (±)-acid (1·5 g.) in aqueous acetone (50 c.c. of 75%). The crystals obtained overnight (1·4 g.), m. p. 125—132°, were twice recrystallised from the same solvent, to give needles (0·8 g.), m. p. 135—137°.

The racemic acid (20 g.) and brucine (45 g.) were dissolved in hot aqueous acetone (200 c.c. of 75%), and the cooled solution inoculated with a crystal of the previously prepared salt. After 2 days the crystals were removed by filtration, providing needles, m. p. 135—137° (19 g.). Decomposition gave the (+)-acid (plates; 4·0 g.) which, after recrystallisation from ligroin, had m. p. 87·5—88·5°, $[\alpha]_D^{19}$ +25·1° (*l*, 2; *c*, 2·43 in chloroform).

The mother-liquors containing the (−)-acid were concentrated to dryness *in vacuo*. The resulting solid (33 g.) was recrystallised three times from aqueous ethanol (75%), when plate-like crystals (17 g.) of m. p. 127—129° were obtained. Decomposition of the salt with dilute hydrochloric acid gave the (−)-acid (3·0 g.) as platelets, m. p. 88—89° (after recrystallisation from chloroform–ligroin), $[\alpha]_D^{18\cdot5}$ −25·7° (*l*, 2; *c*, 2·54 in chloroform).

Decarboxylation of (+)- *and* (−)-*α-Benzyl-α-cyanopropionic Acids*.—(i) The acid (2 g.) of $[\alpha]_D^{19}$ +25·1°, contained in a small distillation flask, was heated at 165°/18 mm. until distillation ceased (about 1 hour). The product was washed with dilute sodium hydrogen carbonate in the usual manner, and found to be devoid of optical activity in the homogeneous state (*l*, 0·5) and in ethereal solution (*l*, 2; *c*, 8·4).

(ii) The experiment was repeated with the (−)-acid (2 g.), and the decarboxylation product was again found to be optically inactive in the homogeneous state (*l*, 0·5) and in ethereal solution (*l*, 2; *c*, 9·2).

The two distillates were combined and redistilled, having b. p. 125—127°/15 mm., n_D^{25} 1·5091. (±)-*α-Benzylpropionitrile* was a colourless oil (Found: C, 83·1; H, 7·6; N, 9·7. $C_{10}H_{11}N$ requires C, 82·9; H, 7·6; N, 9·7%). The nitrile was converted into (±)-α-benzylpropionamide by hydrolysis. This formed needles, m. p. and mixed m. p. 104·5—105·5°.

Thermal Stability of (+)-α-Benzylpropionitrile.—Ethylbenzylmalonate was prepared by a modification of the normal method due to Phillips (*Ind. Chem.*, 1945, **21**, 678), whereby sodium ethoxide was added to a mixture of ethyl malonate and benzyl chloride. The product (86%) had b. p. 168·5—169·5°/12 mm., n_D^{26} 1·4880. This ester was converted into ethyl benzylmethylmalonate in the usual manner (yield 96%; b. p. 179—180°/23 mm.; $n_D^{20\cdot4}$ 1·4863). The last was hydrolysed to benzylmethylmalonic acid (yield 96%, crude), and this acid was decarboxylated to (±)-α-benzylpropionic acid (92%), which solidified after distillation (b.p. 174—176°/30 mm.) to needles, m. p. 35—36°.

(±)-Benzylmethylacetic acid was resolved by Kipping and Hunter's method (*J.*, 1903, 1005). Two recrystallisations from aqueous ethanol gave the quinine salt as needles, m. p. 109—110°, from which (+)-benzylmethylacetic acid of a_D^{19} +13·40° (*l*, 1), n_D^{25} 1·5126, b. p. 167—169°/23 mm. was obtained in 38% yield.

The (+)-acid (45 g.) was converted into (+)-benzylpropionyl chloride (86%), b. p. 120—122°/20 mm., by means of thionyl chloride. The acid chloride was converted by treatment with ammonia solution into (+)-benzylpropionamide, needles (78%) (from aqueous ethanol), m. p. 105—106°, $[\alpha]_D^{20}$ +26·4° (*l*, 2; *c*, 0·592 in ether).

The (+)-amide (26 g.) was distilled with phosphoric oxide (28 g.) under reduced pressure, crude (+)-α-benzylpropionitrile (24 g.) being obtained. Purification and redistillation gave the (+)-nitrile as a colourless oil (20 g., 86%), n_D^{28} 1·5091, a_D^{21} +21·96° (*l*, 1), b. p. 127—128°/17 mm.

A specimen of the nitrile (3 g.) was heated under reflux (oil-bath) at 160—170° for 3 hours. The product was slightly yellow and showed a_D^{21} 21·98°, n_D^{26} 1·5091, before and after distillation, b. p. 127—128°/17 mm.

The nitrile (3·0 g.) was kept at room temperature for several months in concentrated hydrochloric acid (15 c.c.). The product was diluted with an equal volume of water and extracted 3 times with ether. The ethereal extracts were extracted 3 times with sodium hydrogen carbonate solution, and the acidic component was re-extracted with ether after acidification. Evaporation of the dried (Na_2SO_4) ethereal extract yielded (+)-*α-benzylpropionic acid* (2·1 g.), a_D^{21} +13·52° (*l*, 1), n_D^{25} 1·5134 (Found: equiv., 166·1. $C_{10}H_{12}O_2$ requires equiv., 164·2). Hence an approximate value for the rotation of optically pure α-benzylpropionitrile is a_D^{21} 33° (*l*, 1), calculated on optically pure benzylmethylacetic acid.

Thanks are expressed to Imperial Chemical Industries Limited for a grant, and one of the authors (W. A. R.) acknowledges the award of a maintenance grant from the Department of Scientific and Industrial Research.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, June 28th*, 1951.]

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750. *Non-catalytic Reduction of Thiophens. Part II.* 2-Methylthiophen, 3-Methylthiophen, and 2 : 5-Dimethylthiophen.*

By S. F. BIRCH and D. T. MCALLAN.

2-Methylthiophen and 3-methylthiophen, on reduction in liquid ammonia solution by sodium in the presence of methanol, each yield two isomeric dihydromethylthiophens. Pentenethiols are formed as secondary products and the isolation of hydrogen sulphide as an end-product indicates that still further reduction occurs. The structure of the hitherto unknown dihydromethylthiophens has been established by oxidation to known sulphones and by preparation of other derivatives. No dihydrodimethylthiophens were obtained when 2 : 5-dimethylthiophen was reduced under similar conditions, the main product consisting of a mixture of hexenethiols. Ketones have been identified as products of the sodium–methanol reduction of 2-methylthiophen and 2 : 5-dimethylthiophen, and a possible mechanism for their formation is given.

THE non-catalytic reduction of thiophen in liquid ammonia solution by sodium metal in the presence of methanol has already been discussed (Birch and McAllan, *J.*, 1951, 2556 *). Under these conditions, thiophen yielded the two isomeric dihydrothiophens as primary products. Concomitant reactions gave *n*-butenethiols as secondary, and *n*-butenes and hydrogen sulphide as end-products. The present paper describes the application of this non-catalytic method to the reduction of the two methylthiophens and 2 : 5-dimethylthiophen. Throughout this work, conditions were employed favouring the production of optimum yields of the dihydro-compounds and no experimental work was carried out on reaction variables.

The reduction of 3-methylthiophen, with sodium equivalent to 1 mol. of hydrogen, closely paralleled the reduction of thiophen (Part I). The main products were a mixture of dihydro-3-

* Part I, *J.*, 1951, 2556.

methylthiophens (44·7%) and pentenethiol (10%). The total recovery (82·5%) indicated that further reduction had occurred and, on acidification of the extracted alkaline solution much hydrogen sulphide was evolved. Comparison with the reduction of thiophen suggests that substitution in the 3-position favours increased yields of the dihydro-intermediates.

Fractionation of the crude dihydro-3-methylthiophens at atmospheric pressure in an atmosphere of nitrogen yielded 4 : 5-dihydro- and 2 : 5-dihydro-3-methylthiophen. No evidence was obtained of the presence of the third theoretically possible isomer, 2 : 3-dihydro-3-methylthiophen. The 4 : 5-dihydro-compound was much more stable than 2 : 3-dihydro-isomer since it could be distilled at atmospheric pressure in a metal-packed column without undue polymerisation. It did, however, deposit a small amount of solid polymer after several weeks' storage; the 2 : 5-isomer showed slight opalescence after a similar time.

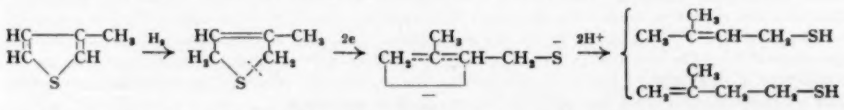
Although the sulphones corresponding to both these dihydro-3-methylthiophens are known (α- and β-isoprene sulphones), only one reference to the preparation of a dihydro-3-methylthiophen itself could be found. Karrer and Kieso (*Helv. Chim. Acta*, **1944**, **27**, 1285) claimed to have obtained such a product by dehydrobromination of 3-bromo-3-methylthiophan with refluxing sodium methoxide solution. Their supposed dihydro-3-methylthiophen boiled at 108—110°, but, as the two isomers now described both boil appreciably higher, there can be little doubt that their compound was not that claimed.

The identification of the two isomeric dihydro-3-methylthiophens followed from their conversion into known sulphones. The sulphone from 2 : 5-dihydro-3-methylthiophen has been prepared by *inter al.* Eigenberger (*J. pr. Chem.*, **1930**, **127**, 307; **1931**, **129**, 312) and Zuydewijn (*Rec. Trav. chim.*, **1937**, **56**, 1047; **1938**, **57**, 445), by the 1 : 4- addition of sulphur dioxide to isoprene. Zuydewijn (*loc. cit.*) characterised this sulphone by converting it into the dibromide by addition of bromine in carbon tetrachloride solution. The sulphone derived from 2 : 5-dihydro-3-methylthiophen by the action of hydrogen peroxide in glacial acetic acid solution had a melting point corresponding to Zuydewijn's compound, as did also the dibromide derived from it.

The sulphone from 4 : 5-dihydro-3-methylthiophen was obtained by Zuydewijn from the 2 : 5-derivative by isomerisation in aqueous alkaline solution under the influence of ultra-violet light. The sulphone from 3-methylthiophen agreed in melting point with that of Zuydewijn and likewise gave a liquid dibromide. The constitution of this sulphone as the 4 : 5-dihydro-isomer and not the 2 : 3-dihydro-isomer was proved by Zuydewijn (*loc. cit.*) through oxidation to 3-ketobutane-1-sulphonic acid. Confirmatory evidence was obtained by Backer, Strating, and Zuithoff (*Rev. Trav. chim.*, **1936**, **55**, 761) who synthesised this acid and compared it with an α-isoprene sulphone-derived sample. They also made a study of the crystallographic data of the barium salts of both samples of acids and found them to be identical.

Both methiodides and mercuric chloride complexes were prepared from each of the dihydro-3-methylthiophens, those prepared from 4 : 5-dihydro-3-methylthiophen being relatively unstable. Bromine added readily to both isomers in *iso*pentane solution and 2 : 5-dihydro-3-methylthiophen gave a solid tetrabromide, with two ionisable bromine atoms, which decomposed to a red oil in 3 days; this is undoubtedly 1 : 1 : 3 : 4-tetrabromo-3-methylthiophan. 4 : 5-Dihydro-3-methylthiophen also added four bromine atoms but yielded only a dark red oil which immediately decomposed with evolution of hydrogen bromide. The behaviour of the dihydro-3-methylthiophens thus parallels that of the corresponding dihydrothiophens (cf. Part I).

The unsaturated pentenethiol obtained from 3-methylthiophen distilled, without polymerisation, as a colourless evil-smelling oil and appeared to be much more stable than the butenethiols. It formed a solid 2 : 4-dinitrophenylpentenyl sulphide and appeared to be substantially free from isomers. A study of the infra-red absorption spectrogram suggested that this thiol, derived from 3-methylthiophen, was formed by the reduction of 2 : 5-dihydro-3-methylthiophen and consisted mainly of 3-methylbut-2-enethiol, together with smaller amounts of 3-methylbut-3-enethiol, formed by isomerisation of the Δ^2-thiol *via* a mesomeric anion.



The reduction of 2-methylthiophen yielded only a small amount of dihydro-2-methylthiophens (7·5%) and a high yield of pentenethiol (38%). The considerable evolution of hydrogen sulphide on acidification of the aqueous alkaline solution indicated that the reduction had proceeded

largely to completion and this would account for the relatively low total recovery (66%). Fractionation of the neutral product yielded an inseparable mixture of 2 : 5-dihydro-2-methylthiophen and most probably 4 : 5-dihydro-2-methylthiophen. On comparing the ratio of reduction products obtained from 2-methylthiophen with those from thiophen and 3-methylthiophen, it is apparent that substitution in the 2-position inhibits the production of dihydro-compounds and favours more complete reduction. Under the conditions employed, the dihydro-2-methylthiophens appear to be preferentially reduced on formation, resulting in a high yield of pentenethiol and end-products.

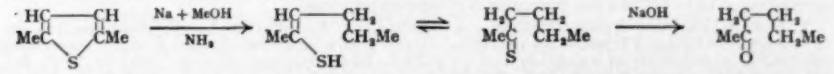
The identification of the individual components of the dihydro-2-methylthiophen fraction was accomplished by oxidation, with excess of hydrogen peroxide, to the sulphone. At 120° the purified sulphone partially decomposed to sulphur dioxide and a highly-unsaturated hydrocarbon, which boiled at about 40°. The residue solidified and, when crystallised to constant melting point, gave analytical data agreeing with a dihydromethylthiophen dioxide. Now Craig (*J. Amer. Chem. Soc.*, 1943, **65**, 1006) obtained 2 : 5-dihydro-2-methylthiophen 1 : 1-dioxide by the reaction of piperylene with sulphur dioxide. The resultant sweet, water-soluble oil, on heating at 100°, decomposed to sulphur dioxide and *trans*-piperylene (b. p. 41·7°). Therefore the dihydro-2-methylthiophen fraction must have contained a proportion of the 2 : 5-dihydro-compound, together with another isomer which could be either 4 : 5-dihydro-2-methylthiophen or 2 : 3-dihydro-2-methylthiophen. By analogy with the behaviour of 3-methylthiophen on reduction, it is concluded that the second isomer was 4 : 5-dihydro-2-methylthiophen. An examination of the infra-red absorption spectrogram of the original fraction yielded some additional evidence in support of this conclusion.

Bromine added readily to the mixed isomers in *iso*pentane solution, in a quantity equivalent to four atoms of bromine per molecule. Much hydrogen bromide was evolved and the product consisted of an unstable red oil, whose carbon tetrachloride solution deposited some yellow crystals. Analysis confirmed the presence of four bromine atoms per molecule, two of them ionisable. In view of the stability of the bromine addition compounds derived from 2 : 5-dihydrothiophen and 2 : 5-dihydro-3-methylthiophen, this solid tetrabromide must be 1 : 1 : 3 : 4-tetrabromo-2-methylthiophan, derived from 2 : 5-dihydro-2-methylthiophen, and the remainder of the unstable red oil the unstable dibromide derived from 4 : 5-dihydro-2-methylthiophen.

The thiol from 2-methylthiophen was a malodorous red oil analysis of which showed it to be a pentenethiol. The 2 : 4-dinitrophenylpentenyl sulphide was an oil which could not be induced to crystallise, indicating that the sample was a mixture of isomers. The thiol polymerised rapidly and distilled over a wide range leaving a viscous residue of high refractive index. No further work was carried out on the identification of the components of this pentenethiol mixture.

In view of the abnormal behaviour of 2-methylthiophen, the reduction of 2 : 5-dimethylthiophen was investigated. It proceeded smoothly, and the product consisted of neutral oil (37·2%) and unsaturated thiol (48%). Fractionation of the neutral product revealed no trace of any dihydro-derivatives, and the distillate was shown to be an azeotrope of unreacted 2 : 5-dimethylthiophen with a small amount of hexan-2-one which was isolated as the semicarbazone. Analysis of the thiol product indicated a hexene compound and, though hydrogen sulphide was identified as an end-product, no corresponding hexenes were isolated. On further reduction of this thiol with excess of sodium, most of it was recovered unchanged and again, though some hydrogen sulphide was evolved, no hexenes were found. However, a neutral fraction (12%) was isolated as a colourless sweet-smelling oil from which a clear distillate and a high-boiling dark residue were obtained. From the former a quantity of hexan-2-one was isolated as the semicarbazone. The presence of this ketone in the reduction products of 2 : 5-dimethylthiophen can be satisfactorily explained as follows :

The crude hexenethiol probably contains some hex-2-ene-2-thiol which is capable of isomerisation to hexane-2-thione from which the ketone can be formed by the action of alkali (*cf.* Bost and Cosby, *J. Amer. Chem. Soc.*, 1935, **57**, 1404) :



These results suggest that small amounts of analogous ketones should have been formed from the other thiophens already reduced. If so, butaldehyde, valeraldehyde and pentan-2-one should be formed from thiophen, 3-methylthiophen, and 2-methylthiophen, respectively.

Whilst these compounds have not yet been detected in any of the recovered thiophens, pentan-2-one has successfully been isolated, as the semicarbazone, from the alkali-insoluble oil obtained by further non-catalytic reduction of the pentenethiol from 2-methylthiophen.

Compound	B. p.	M. p.	Calc. m. p. for zero impurity	n_D^{20}	d^{20}	Estimated purity, mol. %
2-Methylthiophen	112·56°	−63·34°	− 63·37°	1·5201	1·0194	99·95
3-Methylthiophen	115·44	−68·96	− 68·94	1·5202	1·0221	99·95
2 : 5-Dimethylthiophen	137·5	—	—	1·5123	0·9840	—
Dihydro-2-methylthiophens (mixed)	127—128	glass at −120	—	1·5069	1·0140	—
4 : 5-Dihydro-3-methylthiophen	139·4	− 54·7	—	1·5232	1·0055	—
2 : 5-Dihydro-3-methylthiophen	147·5	− 32·12	− 31·2	1·5196	1·0160	98·5
2-Methylthiophan	133·23	−100·79	−100·71	1·4909	0·9552	99·75
3-Methylthiophan	138·67	− 81·26	− 81·16	1·4924	0·9634	99·7
trans-2 : 5-Dimethylthiophan	142·0 *	− 76·70	− 76·35	1·4776	0·9177	99·3
cis-2 : 5-Dimethylthiophan	142·28	− 89·60	− 89·4	1·4799	0·9222	99·3

* This is an extrapolated figure owing to the thermal instability of the compound at atmospheric pressure.

The physical properties of the various dihydromethylthiophens, together with those of the corresponding thiophens and thiophans, determined during this research, are given in the table.

Experimental

Analyses are by Weiler and Strauss, Oxford. All m. p.s and b. p.s are corrected.

Preparation of Dihydro-3-methylthiophens.—3-Methylthiophen (392 g., 4 mols.) and methanol (1500 ml.), in liquid ammonia (*ca.* 1500 ml.), were treated with sodium (185 g., 8 mols.) exactly as described for the preparation of the dihydrothiophens (Part I, *loc. cit.*). Neutral products were extracted into *iso*pentane as previously described; the evil-smelling thiol fraction distilled almost completely in the range 40—43°/35 mm. (135—138°/760 mm.) and had n_D^{20} 1·4840 (Found: C, 59·7; H, 9·5; S, 30·5. Calc. for $C_5H_{10}S$: C, 58·8; H, 9·9; S, 31·4%). A solid 2 : 4-dinitrophenylpentenyl sulphide was obtained and repeatedly crystallised from ethanol, forming a pale yellow flocculent powder, m. p. 113—115°.

A large quantity of 3-methylthiophen (1250 g.) was reduced in this manner yielding recovered 3-methylthiophen (346 g., 27·7%), crude pentenethiol (130 g.; 10%), and a mixture of dihydro-3-methylthiophens (570 g., 44·7%), b. p. 138—148°/760 mm. This mixture, on fractionation through a 50-plate metal-packed column under an atmosphere of nitrogen, gave 4 : 5-*dihydro-* (84 g.), b. p. 139·4°/760 mm., n_D^{20} 1·5232 (Found: C, 59·9; H, 8·2; S, 31·5. C_5H_8S requires C, 60·0; H, 8·1; S, 32·0%), and 2 : 5-*dihydro-3-methylthiophen* (400 g.), b. p. 147·5°/760 mm., n_D^{20} 1·5196 (Found: C, 60·0; H, 8·1; S, 31·7%).

2 : 5-Dihydro-3-methylthiophen yielded a *mercuric chloride* complex (from ethanol), m. p. 127·5—128·0° (Found: C, 16·8; H, 2·3; S, 9·4; Cl, 20·9. $C_5H_8S,HgCl_2$ requires C, 16·2; H, 2·2; S, 8·9; Cl, 20·1%). The *methiodide*, crystallised from ethanol at low temperature, formed needles, m. p. 91—92°, which were unstable on exposure to air and so gave an indifferent analysis (Found: C, 30·3; H, 4·7; S, 10·1; I, 54·7. C_5H_8S,CH_3I requires C, 29·8; H, 4·6; S, 13·2; I, 52·4%).

The 4 : 5-dihydro-isomer yielded a *mercuric chloride* complex (from ethanol) as a yellowish white solid, m. p. 93—94° (decomp.), the analysis of which did not correspond to any simple empirical formula (Found: C, 14·6; H, 2·0; S, 6·2; Cl, 20·9%). The methiodide was obtained as an unstable liquid which solidified only at very low temperature, and no analysis was possible.

Identification of 2 : 5-Dihydro-3-methylthiophen.—Oxidation to 2 : 5-dihydro-3-methylthiophen 1 : 1-dioxide (β-isoprene sulphone). A 50% excess of hydrogen peroxide (30 ml.; 100-vol.) was added to 2 : 5-dihydro-3-methylthiophen (10 g.) in glacial acetic acid (60 ml.) and, after 24 hours at room temperature, the solution was refluxed for 3 hours to destroy excess of peroxide. Removal of the solvent on the water-bath at reduced pressure left a solid which crystallised from benzene–light petroleum as small needles, m. p. 63—64° (Found: C, 45·2; H, 6·2; S, 24·6. Calc. for $C_5H_8O_2S$: C, 45·4; H, 6·1; S, 24·3%). Zuydewijn (*loc. cit.*) gave the m. p. of β-isoprene sulphone as 63—64°.

3 : 4-*Dibromo-3-methylthiophan* 1 : 1-*dioxide*. The sulphone (2 g.) was refluxed in carbon tetrachloride (50 ml.) for 1 hour with the requisite amount of bromine. White plates separated; after three crystallisations from carbon tetrachloride these had m. p. 125—126° (Found: C, 20·4; H, 2·7; S, 11·2; Br, 53·8. Calc. for $C_5H_8O_2SBr_2$: C, 20·6; H, 2·8; S, 11·0; Br, 54·7%). Zuydewijn (*loc. cit.*) recorded m. p. 125—127° for the dibromide of β-isoprene sulphone.

1 : 1 : 3 : 4-*Tetrabromo-3-methylthiophan*. A solution of 2 : 5-dihydro-3-methylthiophen in *iso*pentane added 4 atoms of bromine per molecule to give a yellow *tetrabromo*-compound which crystallised from carbon tetrachloride as orange crystals, m. p. 98·5—99·0° (decomp.) (Found: total Br, 76·0; Br′, 40·0. $C_5H_6SBr_4$ requires total Br, 76·1; Br′, 38·1%). This solid decomposed to a red oil during 3 days.

Identification of 4 : 5-Dihydro-3-methylthiophen.—Oxidation to 4 : 5-dihydro-3-methylthiophen 1 : 1-dioxide (α-isoprene sulphone). A solution of the isomer (10 g.) in glacial acetic acid (60 ml.) was oxidised by hydrogen peroxide (30 ml.; 100-vol.) as previously described. After removal of the solvent, the

residue was dissolved in hot benzene from which white needles were precipitated on the addition of light petroleum. Recrystallisation from benzene–light petroleum yielded the sulphone as long white needles, m. p. 77—78° (Found: C, 45·6; H, 6·2; S, 24·4%). For α-isoprene sulphone Zuydewijn (*loc. cit.*) gave m. p. 76—77°, and Eigenberger (*loc. cit.*) gave m. p. 77·5—78·0°.

Attempts to prepare 2 : 3-dibromo-3-methylthiophan 1 : 1-dioxide and 1 : 1 : 2 : 3-tetrabromo-3-methylthiophan, by the methods used for the preparation of their isomers from 2 : 5-dihydro-3-methylthiophen, were unsuccessful.

Preparation of Dihydro-2-methylthiophens.—2-Methylthiophen (392 g.; 4 mols.) was reduced with sodium (185 g.; 8 mols.) and methanol (1500 ml.) in liquid ammonia (*ca.* 1500 ml.) at −40°. Two runs on this scale yielded neutral product (225 g.; 28·7%) and unsaturated thiol (309 g., 37·8%). There was considerable evolution of hydrogen sulphide on acidification of the aqueous solution to recover the thiol, and the low recovery of product was partly due to this further reduction. The thiol was a malodorous oil, which quickly developed a bright red colour (Found: C, 58·9; H, 9·5; S, 30·4. Calc. for $C_5H_{10}S$: C, 58·8; H, 9·9; S, 31·4%). The product of reaction with 1-chloro-2 : 4-dinitrobenzene was an oil which would not crystallise. Only 27% of the thiol boiled in the range 35—56°/25 mm., n_D^{20} 1·4610; the residue was a viscous red oil, n_D^{20} 1·5454.

The neutral product was fractionated in a 20-plate glass-packed column and yielded recovered 2-methylthiophen (150 g., 19%) and a mixture of dihydro-2-methylthiophens (60 g., 7·5%), the main fraction (40 g., 5%) of which had b. p. 127—128°, n_D^{20} 1·5069 (Found: C, 59·8; H, 8·1; S, 31·8%), and set to a glass at −120°; all attempts to prepare a solid methiodide and a solid mercuric chloride complex failed.

Identification of the Dihydro-2-methylthiophens.—Oxidation to the sulphone. A portion of the dihydro-2-methylthiophen fraction (10 g.) was oxidised with hydrogen peroxide in acetic acid as described previously. When the solution was refluxed to destroy excess of peroxide, some sulphur dioxide was evolved and a small amount of unsaturated low-boiling hydrocarbon was isolated during the removal of the solvent. The residue was a dark oily mass which smelt faintly of sulphur dioxide. The oxidation was accordingly modified: the solution was set aside for 72 hours before removal of the solvent at low pressure at a maximum of 50°. The residual pale oil was precipitated from benzene solution by light petroleum. The oil was heated at 120° for a few minutes under reduced pressure and, from a liquid-air trap attached to the apparatus, sulphur dioxide and a highly-unsaturated hydrocarbon, b. p. *ca.* 40°, were obtained. The dark residue crystallised from ethanol as needles, m. p. 128—129° after three crystallisations (Found: C, 45·7; H, 6·1; S, 24·2. $C_5H_8O_2S$ requires C, 45·4; H, 6·1; S, 24·3%). Now Craig (*loc. cit.*) obtained 2 : 5-dihydro-2-methylthiophen 1 : 1-dioxide (piperylene sulphone) as an oil which decomposed at 100° into sulphur dioxide and *trans*-piperylene, b. p. 41·7°, and so the dihydro-2-methylthiophen mixture undoubtedly contains some 2 : 5-dihydro-2-methylthiophen, together with another isomer which yields a sulphone, m. p. 128—129°. This isomer may be the 2 : 3-dihydro- or the 4 : 5-dihydro-compound, but, in view of the double-bond positions in the dihydro-3-methylthiophens, it is assumed that the second isomer is 4 : 5-dihydro-2-methylthiophen.

Addition Compound with Bromine.—The addition of bromine to an *iso*pentane solution of the dihydro-2-methylthiophen mixture proceeded rapidly, with evolution of hydrogen bromide, till 4 bromine atoms per molecule had been absorbed. A red oil separated, and was dissolved in hot carbon tetrachloride from which a small amount of yellow solid, m. p. 90° (decomp.), crystallised. By analogy with the tetrabromides from 2 : 5-dihydrothiophen and 2 : 5-dihydro-3-methylthiophen this is probably 1 : 1 : 3 : 4-*tetrabromo-2-methylthiophan*. Analysis indicated the presence of 4 bromine atoms per molecule, 2 of which were ionisable (Found: total Br, 75·9; Br′, 38·7. $C_5H_8SBr_4$ requires total Br, 76·1; Br′, 38·1%). The original crude red oil was probably a mixture with the unstable tetrabromide derived from 2-methyl-4 : 5-dihydrothiophen.

2 : 3-*Dibromo-2-methylthiophan* 1 : 1-*Dioxide.*—4 : 5-Dihydro-2-methylthiophen 1 : 1-dioxide (0·5 g.) was dissolved in an aqueous solution of the requisite amount of bromine, and set aside at 0° for 4 days. Long needles of 2 : 3-*dibromo-2-methylthiophan* 1 : 1-*dioxide*, m. p. 68—69°, separated (Found: C, 20·9; H, 2·4; S, 10·9; Br, 54·2. $C_5H_8O_2SBr_2$ requires C, 20·6; H, 2·8; S, 11·0; Br, 54·7%).

Reduction of 2 : 5-*Dimethylthiophen.*—2 : 5-Dimethylthiophen, prepared in 51% yield by Buu-Hoï and Nguyen-Hoán's method (*Rec. Trav. chim.*, 1948, **67**, 309), had b. p. 137·5°, n_D^{20} 1·5123. The dimethylthiophen (336 g.; 3 mols.) was reduced with sodium (140 g., 6 mols.) and methanol (1000 ml.) in liquid ammonia (1500 ml.) at −40°, as previously described. The reaction proceeded smoothly. The combined product from two such preparations yielded neutral material (250 g., 37·2%) and crude hexenethiol (335 g.; 48%), n_D^{20} 1·5335 (Found: C, 62·9; H, 8·9; S, 27·5. Calc. for $C_6H_{12}S$: C, 62·0; H, 10·4; S, 27·6%). Distillation at reduced pressure under nitrogen gave only 24% boiling in the range 56—60°/16 mm., (n_D^{20} 1·5030), and a further 9% at 60—100°/16 mm., (n_D^{20} 1·5200), leaving a high-boiling viscous residue (n_D^{20} 1·5570). These fractions had a typical unsaturated-thiol odour somewhat tempered by a relatively sweet background-odour; they showed a colour variation from purple to orange, and the residue was bright red.

The neutral material was fractionated at reduced pressure under nitrogen in a 20-plate glass-packed column, yielding a main fraction, b. p. 79°/130 mm., n_D^{20} 1·5050, but no material was isolated at or above the b. p. and refractive index of the original 2 : 5-dimethylthiophen. A freezing-point determination indicated the presence of a substantial amount of impurity and, as washing the fractions with concentrated alkaline solutions did not alter the physical constants, the distillate was refractionated in a 50-plate metal-packed column at atmospheric pressure. The maximum b. p. and refractive index then reached were 137·0° and n_D^{20} 1·5070, while some of the fore-runnings had refractive indices as low as n_D^{20} 1·4620. The neutral product thus appeared to be an azeotrope of unchanged 2 : 5-dimethylthiophen

with an unknown product of similar b. p. The fore-runnings (12 g.), n_D^{20} 1·4620, were subsequently shaken in light petroleum solution with a saturated aqueous solution of semicarbazide hydrochloride and an equivalent of sodium acetate. Hexan-2-one semicarbazone (7 g.) separated and was repeatedly crystallised from aqueous alcohol; it had m. p. and mixed m. p. 122—123° (Found: C, 53·1; H, 9·4; N, 26·1. Calc. for $C_7H_{15}ON_3$: C, 52·8; H, 9·5; N, 26·4%).

Reduction of the Hexenethiol derived from 2 : 5-*Dimethylthiophen.*—Crude hexenethiol (116 g., 1 mol.) was reduced with excess of sodium (70 g., 3 mols.) and methanol (500 ml.) in liquid ammonia (750 ml.) at −40°. The products of the slow reaction were obtained as already described; unchanged thiol (77 g., 67·3%), n_D^{20} 1·4960, was recovered and the neutral fraction contained no hexenes. The residue (13 g.) was distilled under nitrogen at reduced pressure, yielding a clear distillate (5 g.), b. p. 55—62°/50 mm., n_D^{20} 1·4290, and a high-boiling residue which decomposed when heated further. The distillate clearly contained oxygenated compounds [Found: C, 71·3; H, 12·1; S, 7·5; O (by difference) 9·1%], and subsequent treatment with aqueous semicarbazide hydrochloride and sodium acetate solution gave hexan-2-one semicarbazone, which crystallised from aqueous alcohol and then had m. p. and mixed m. p. 122·5—123·5° (Found: C, 53·3; H, 9·4; N, 25·9. Calc. for $C_7H_{15}ON_3$: C, 52·8; H, 9·5; N, 26·4%).

Reduction of the Pentenethiol derived from 2-Methylthiophen.—Crude pentenethiol (102 g., 1 mol.) was reduced as described above. Unchanged thiol (72·5 g., 70%) was recovered as a red oil, n_D^{20} 1·4900. The neutral product (17·5 g.) contained no pentenes but, on treatment with semicarbazide hydrochloride solution, yielded pentan-2-one semicarbazone which crystallised from aqueous methanol and then had m. p. and mixed m. p. 110—111° (Found: C, 50·6; H, 9·0; N, 29·3. Calc. for $C_6H_{13}ON_3$: C, 50·3; H, 9·2, N, 29·4%). An attempt to distil the residual material yielded only a trace of distillate at about 100° before decomposition started.

Our thanks are due to the Chairman of the Anglo-Iranian Oil Company Limited for permission to publish these results. We also thank Mr. W. Crawford for the determination of purities.

ANGLO-IRANIAN OIL CO. LTD., RESEARCH STATION,
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[*Received, July 12th*, 1951.]

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751. *Toluene-*p*-sulphonylhydrazones of the Pentose Sugars, with Particular Reference to the Characterisation and Determination of Ribose.*

By D. G. EASTERBY, L. HOUGH, and J. K. N. JONES.

Toluene-*p*-sulphonylhydrazones of L-arabinose, D-ribose, D-xylose, D-lyxose, and L-fucose have been prepared in good yield and form useful derivatives for characterisation of these sugars. Under standard conditions, the formation of crystalline D-ribose toluene-*p*-sulphonylhydrazone is quantitative and may be used for the determination of D-ribose. The optical rotatory powers of solutions of these derivatives in dry pyridine, and in pyridine containing small amounts of water and acid, have been studied.

AMONGST the pentose sugars, D-ribose occupies a unique position in that it is a component of the nucleic acids, found in all animal and plant cells, and of certain coenzymes and vitamins. The characterisation and determination of ribose are, therefore, of considerable importance. Crystalline derivatives of ribose have been described; for example, ribosebenziminazole (Dimler and Link, *J. Biol. Chem.*, 1943, **150**, 345), ribose "diphenylmethane-dimethyl-dihydrazone" (von Braun, *Ber.*, 1913, **46**, 3949), and ribose diethyl thioacetal (Kenner, Rhodda, and Todd, *J.*, 1949, 1613). Ribose has been determined hitherto either by conversion into furfuraldehyde, which may be determined as the phloroglucide (Schorger, *Ind. Eng. Chem.*, 1928, **15**, 748; Dorée, "Methods of Cellulose Chemistry," Chapman and Hall, London, 1947, p. 381), by colorimetric methods (cf. Dunstan and Gillam, *J.*, 1949, S 140; Barker, *J.*, 1950, 1636), or by separation on the paper partition chromatogram and subsequent estimation by sodium metaperiodate (Hirst and Jones, *J.*, 1949, 1659) or colorimetrically by use of aniline phthalate (Blass, Macheboeuf, and Nunez, *Bull. Soc. Chim. biol.*, 1950, **32**, 130).

We have observed that ribose readily yields a highly crystalline toluene-*p*-sulphonylhydrazone, which is sparingly soluble in methanol, ethanol, or water, the normal solvents for sugars. The reagent, toluene-*p*-sulphonhydrazide is a crystalline solid and possesses the advantages

of stability and ease of preparation. Calibration with varying quantities of D-ribose showed that, under standard conditions, the formation of the toluene-*p*-sulphonylhydrazone is quantitative and thus affords a gravimetric procedure for the determination of ribose (see Table, p. 3418). The reaction is not, however, specific, since arabinose, xylose, lyxose, and fucose readily yield crystalline toluene-*p*-sulphonylhydrazones in good yield under these conditions and will, therefore, interfere with the determination of ribose. This is not a serious drawback, however, since ribose normally does not occur in Nature in admixture with other sugars. Even so, the difficulty may be circumvented by chromatographic separation before the formation of the derivatives. The above toluene-*p*-sulphonylhydrazones form useful derivatives for the characterisation of pentoses, since their preparation is easy and the products may be identified by physical constants and also by fission with dilute acid or by heating them with benzaldehyde, whereafter the liberated pentose may be identified in the usual way on the paper chromatogram.

The use of toluene-*p*-sulphonhydrazide for the characterisation of sugars was first described by Freundenberg and Rümmel (*Annalen*, 1924, **440**, 45), who isolated derivatives of glucose and hamamelose; and, later, Freundenberg and Raschig (*Ber.*, 1929, **62**, 373) formed fucose toluene-*p*-sulphonylhydrazone. This reagent has been used with advantage in conjunction with partition chromatography for the characterisation of arabinose, xylose, and ribose in the complex mixture arising from the condensation of glyceraldehyde with glycollic aldehyde (Hough and Jones, *J.*, 1951, 1122) and for the characterisation of L-fucose in the fission products of linseed mucilage (*Linum usitatissimum*) (Easterby and Jones, unpublished results).

Studies of sugar amine derivatives, stimulated by the occurrence of this type of linkage in the nucleic acids and certain coenzymes, have revealed that they can assume a number of different forms, possibly existing in the α- and β-orientations of both the furanoside and pyranoside modifications, and that, in solution, there is a ready interchange of these various forms, presumably through the acyclic Schiff's base (Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 855; Honeyman and Tatchell, *J.*, 1950, 967; Butler, Laland, Overend, and Stacey, *J.*, 1950, 1433; Ellis and Honeyman, *Nature*, 1951, **167**, 239). Although Honeyman and Tatchell (*loc. cit.*) and Ellis and Honeyman (*loc. cit.*) have pointed out that the existence of the aniline derivative of α-D-ribofuranoside has not yet been firmly established, it has been suggested that this substance is partly converted in moist pyridine into the β-isomer, whereas in pyridine containing acidic catalysts it gives an equilibrium mixture of the αβ-pyranosides; in dry pyridine, mutarotation is arrested and therefore mutarotation occurs only in pyridine containing water or acid (Howard, Kenner, Lythgoe, and Todd, *loc. cit.*). In contrast, D-ribose toluene-*p*-sulphonylhydrazone mutarotates in dry redistilled pyridine ($[\alpha]_D$ + 23° ⟶ +14°), and in moist pyridine, the initial specific rotation is enhanced ($[\alpha]_D$ + 42·5 ⟶ + 16°). On the other hand, xylose and arabinose toluene-*p*-sulphonylhydrazones do not show mutarotation and give approximately the same specific rotation ($[\alpha]_D$ + 3° and −36° respectively) in dry redistilled pyridine and in moist pyridine. However, the addition of a little hydrochloric acid to pyridine solutions of the above derivatives caused a marked change in their optical rotatory power. Thus, the arabinose derivative mutarotated from $[\alpha]_D$ −7° to −13·5° and the xylose derivative gave a constant specific rotation of −14°. Thus, it may well be that the pentose toluene-*p*-sulphonylhydrazones are capable of existing in more than one modification, although there is no evidence available as yet to show whether the molecule is of amino-sugar or of Schiff's base type. In view of the marked effect that a trace of impurity in pyridine has on the initial and final specific rotations of certain of these derivatives, caution should be observed when optical rotatory power is applied to these or analogous derivatives as a criterion of identity or purity.

Experimental.

Unless otherwise stated, dry redistilled pyridine, prepared by distillation from potassium hydroxide pellets, was employed. M. p.s are uncorrected.

General Procedure.—The aldose is dissolved in methanol (10 ml.), to which is then added a solution (10 ml.) of toluene-*p*-sulphonhydrazide in methanol (7 g. in 100 ml.). The solution is heated under reflux on the boiling water-bath for 30 minutes and then stored in the refrigerator. After approx. 20 hours, the crystalline residue is isolated on a tared filter, washed with ice-cold methanol (30 ml.), dried under reduced pressure over silica gel at 80° for 30 minutes, cooled in a desiccator, and weighed.

D-Ribose thus readily gave a crystalline *toluene-p-sulphonylhydrazone*, m. p. 164°, {$[\alpha]_D$ +23° (*c*, 0·7 in pyridine) ⟶ +14° (16 h.); $[\alpha]_D$ +42° (*c*, 1·4 in wet pyridine) ⟶ +14° (17 h.); $[\alpha]_D$ +13° (*c*, 1·4 in pyridine containing a little concentrated hydrochloric acid) ⟶ +9° (24 h.); $[\alpha]_D$ +55° (*c*, 0·86 in commercial pyridine) ⟶ +20° (24 h.)} (Found: C, 45·5; H, 5·5; N, 8·9. $C_{12}H_{16}O_6N_2S$ requires C, 45·3; H, 5·7; N, 8·8%), which was only sparingly soluble in boiling methanol, ethanol, or water.

The results in the table show that solutions (1—4%) of ribose in methanol may be determined with an accuracy of ±1%.

Ribose used (g.)	Yield of derivative (g.)	Ribose found (g.)	Error (g.)	Ribose used (g.)	Yield of derivative (g.)	Ribose found (g.)	Error (g.)
0·038	0·029	0·014	−0·024	0·187	0·389	0·187	0·000
0·083	0·161	0·077	−0·006	0·287	0·586	0·282	−0·005
0·100	0·227	0·109	+0·009	0·377	0·778	0·383	+0·006
0·109	0·226	0·109	0·000				

The effect of adding other sugars, which also give the derivative (see below), was examined. (i) A mixture of D-ribose (0·2808 g.) and L-arabinose (0·0376 g.) in methanol (10 ml.) was treated as above. The crystalline product was removed and, from its weight (0·6273 g.), it is clear that the arabinose has interfered with the estimation of ribose. (ii) D-Ribose (0·1902 g.) and D-xylose (0·0174 g.) were converted into the derivatives as described above and yielded only D-ribose toluene-*p*-sulphonylhydrazone (0·3854 g., 98% yield); hence the xylose has not interfered with the determination. (iii) D-Ribose (0·4148 g.) and D-xylose (0·1586 g.), treated as above, gave only D-ribose toluene-*p*-sulphonylhydrazone (0·6842 g., 75% yield), m. p. and mixed m. p. 164°. Hence, the xylose derivative, although not crystallising with the ribose derivative, has interfered with the determination.

L-Fucose (0·0914 g.) was treated with the reagent as above. The crystalline product (0·1584 g., 70%) was removed, washed with a little ice-cold methanol, and dried, to give fine white needles of L-fucose toluene-*p*-sulphonylhydrazone, m. p. 169°, $[\alpha]_D$ −19° (10 min.; *c*, 2·2 in pyridine) ⟶ −9° (23 h.) (Found: C, 46·9; H, 5·8; N, 8·6. Calc. for $C_{13}H_{20}O_4N_2S$: C, 47·0; H, 6·02; N, 8·4%).

L-Arabinose (0·1280 g.) gave a crystalline *toluene-*p*-sulphonylhydrazone* (0·2104 g., 78%), m. p. 153—154°, $[\alpha]_D$ +3° (*c*, 2·8 in pyridine, const.), $[\alpha]_D$ +2° (*c*, 2·1 in moist pyridine, const.), $[\alpha]_D$ −7° (*c*, 0·89 in pyridine containing a little concentrated hydrochloric acid) ⟶ −13·5° (24 h.) (Found: C, 45·5; H, 5·6; N, 8·9. $C_{12}H_{18}O_4N_2S$ requires C, 45·3; H, 5·7; N, 8·8%).

D-Xylose (0·2338 g.) gave a *toluene-*p*-sulphonylhydrazone* (0·2450 g.) which crystallised as fine, white needles, m. p. 149°, $[\alpha]_D$ −36° (*c*, 1·8 in pyridine, const.), $[\alpha]_D$ −36° (*c*, 1·3 in moist pyridine, const.), $[\alpha]_D$ −14° (*c*, 1·8 in pyridine containing a little concentrated hydrochloric acid, const.), $[\alpha]_D$ −14° (*c*, 1·9 in commercial pyridine) ⟶ −1° (24 h.) (Found: C, 45·1; H, 5·7; N, 9·0. $C_{12}H_{18}O_4N_2S$ requires C, 45·3; H, 5·6; N, 8·8%).

D-Lyxose gave a crystalline *derivative*, m. p. 141° (Found: N, 9·3. $C_{12}H_{18}O_4N_2S$ requires N, 8·8%).

The derivatives of xylose, arabinose, lyxose, and fucose may be recrystallised from methanol. Derivatives of galactose, rhamnose, and fructose could not be obtained by the above procedure.

One of us (D. G. E.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

THE UNIVERSITY, BRISTOL, 8. [*Received, August 10th*, 1951.]

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752. *Synthesis of Plant-growth Regulators. Part I. Substituted β-Naphthyloxyacetic Acids.*

By (MISS) P. M. JAMES and D. WOODCOCK.

A number of mono-, di-, and tri-chloro-, and mononitro-β-naphthyloxyacetic acids have been prepared for examination as parthenocarpic agents. New syntheses of 5-, 7-, and 8-chloro-2-naphthols are described, and a discrepancy in the m. p. of 5-chloro-2-naphthol is reported.

SUBSTITUTED phenoxyacetic acids have a variety of biochemical roles, including rooting agents (Hitchcock and Zimmerman, *Contr. Boyce Thompson Inst.*, 1942, **12**, 497), herbicides (B.P. 573,929/1941; Hamner and Tukey, *Science*, 1944, **100**, 154; Templeman and Sexton, *Proc. Roy. Soc., B*, 1946, **133**, 300; Slade, Templeman, and Sexton, *Nature*, 1945, **155**, 497; Nutman, Thornton, and Quastel, *ibid.*, p. 498; Blackman, *ibid.*, p. 500), and parthenocarpic agents (Zimmerman and Hitchcock, *Contr. Boyce Thompson Inst.*, 1942, **12**, 321). In several of these publications the effect of the number and the position of substituent halogen atoms and nitro-groups on physiological activity is described, and a wide variation noted.

The parthenocarpic activity shown by many of these acids is shared by β-naphthyloxyacetic acid (Gustafson, *Proc. Amer. Soc. Hort. Sci.*, 1943, **40**, 387), and it was decided to investigate

the effect of nuclear chlorine substitution in this case. 1-Chloro-2-naphthyloxyacetic acid has already been described (Templeman and Sexton, *loc. cit.*) and we have prepared the remaining acids by condensing ethyl bromoacetate with the sodium salt of the appropriate naphthol. The 3-, 4-, 6-, and 7-chloro-2-naphthols were obtained by known methods, often with some improvement.

Dilthey, Quint, and Heinen (*J. pr. Chem.*, 1939, **152**, 73) recorded the preparation of 8-chloro-2-naphthol from the corresponding 8-amino-compound by diazotisation, followed by a Sandmeyer reaction using cuprous chloride. Attempts by us to prepare 5- or 8-chloro-2-naphthol using this procedure gave only tars. Similar treatment of 5-amino-2-methoxynaphthalene gave a red oil which on demethylation with hydriodic acid also resulted in the formation of tar. Finally 5- and 8-chloro-2-naphthols were prepared from the nitronaphthyl acetates by successive reduction, Sandmeyer reactions, and hydrolysis. The structure of our 5-chloro-2-naphthol is proved by the method of synthesis and confirmed by its oxidation to 3-chlorophthalic acid by alkaline potassium permanganate; it had m. p. 97—98°, although Claus (*J. pr. Chem.*, 1889, **39**, 317) gives m. p. 128°; his product may have been 7-chloro-2-naphthol, m. p. 126·5° (Franzen and Deibel, *ibid.*, 1908, **78**, 154).

The only dichloro-2-naphthyloxyacetic acid previously described is the 1 : 6-compound which is reported to have been obtained by direct chlorination of the unsubstituted acid at 60° (Haskelberg, *J. Org. Chem.*, 1947, **12**, 426). Repetition of this work gave 1 : 4-dichloro-2-naphthyloxyacetic acid, m. p. 188—189°, identical with that prepared from 1 : 4-dichloro-2-naphthol (James and Woodcock, *J.*, 1951, 1931). Attempts to obtain 1 : 6-dichloro-2-naphthol have already been described (James and Woodcock, *loc. cit.*) and there is no reliable evidence to support the view that it is formed in the direct chlorination of 1-chloro-2-naphthol. In addition to the 1 : 4-dichloro-acid, 1 : 3- and 3 : 4-dichloro- and 1 : 3 : 4-trichloro-2-naphthyloxyacetic acids were also obtained from the corresponding naphthols. The acids reported in this paper have been tested for parthenocarpic activity by Dr. L. C. Luckwill, using unpollinated tomato ovaries (Luckwill, *J. Hort. Sci.*, 1948, **24**, 19), and the results will be fully reported elsewhere.

Experimental.

M. p.s are uncorrected. Carbon and hydrogen analyses were by Drs. Weiler and Strauss, Oxford.

3-Chloro-2-naphthol.—In Marschalk's method of preparation (*Bull. Soc. chim.*, 1928, **43**, 1361), isolation is improved by steam-distillation at the final stage.

4-Chloro-2-naphthol.—This was obtained in 77% yield by the reduction of 1 : 4-dichloro-2-naphthol using stannous chloride and hydrochloric acid (cf. Burton, *J.*, 1945, 282).

6-Chloro-2-naphthol.—6-Amino-2-naphthol-4-sulphonic acid (10 g.) (Ruggli *et al.*, *Helv. Chim. Acta*, 1929, **12**, 1051) was diazotised and the solution decomposed by dropwise addition to cuprous chloride (6·7 g.) in boiling concentrated hydrochloric acid (60 ml.). After removal of the copper with hydrogen sulphide, the solution was evaporated to half-bulk and stirred during the portionwise addition of sodium amalgam (400 g.; 4%) and concentrated hydrochloric acid (80 ml.). The crude dark product which separated was collected and purified by dissolving it in a minimum amount of 2N-sodium hydroxide, filtration, addition of 2N-hydrochloric acid to cloudiness, shaking with charcoal, filtration, and final acidification with acetic acid. The product crystallised from water in needles (3·2 g.), m. p. 114—115° (Found : Cl, 19·9. Calc. for $C_{10}H_7OCl$: 19·9%). Ruggli *et al.* give m. p. 115°. The *acetate*, prepared in the usual way crystallised from methyl alcohol in prisms, m. p. 100—101° (Found : C, 65·2; H, 4·2; Cl, 16·0. $C_{12}H_9O_2Cl$ requires C, 65·3; H, 4·1; Cl, 16·1%).

2 : 7-Dinitronaphthalene.—Clemo and Driver (*J.*, 1945, 829) reported poor yields from the decarboxylation of 3 : 6-dinitronaphthalic anhydride and abandoned the method. In our hands this route gave a 60% yield of 2 : 7-dinitronaphthalene, m. p. 229—230°, suitable for conversion without further purification into 7-nitro-2-naphthylamine.

2-Chloro-7-nitronaphthalene.—Diazotisation of 7-nitro-2-naphthylamine (Hodgson and Ward, *J.*, 1945, 590), followed by a Sandmeyer reaction using cuprous chloride, resulted in a 97% yield of the chloro-compound. This crystallised from ethyl alcohol in brownish prisms, m. p. 139—140° (Found : Cl, 17·3. Calc. for $C_{10}H_6O_2NCl$: 17·1%). Hodgson and Ward (*J.*, 1947, 330) give m. p. 136°.

7-Chloro-2-naphthylamine.—2-Chloro-7-nitronaphthalene (7·5 g.), suspended in ethyl alcohol (100 ml.) and shaken in hydrogen in the presence of Raney nickel, rapidly absorbed the theoretical amount of hydrogen. The filtered solution was concentrated to ½-bulk, water (5 ml.) added, and the solution chilled to 0°. The product (4·4 g.) crystallised from aqueous ethyl alcohol in prisms, m. p. 120—121° (Found : Cl, 19·8. Calc. for $C_{10}H_8NCl$: 20·0%). Hodgson and Ward (*loc. cit.*) give m. p. 118—119°. The *acetate*, prepared in the usual way, crystallised from aqueous methyl alcohol in plates, m. p. 101—102° (Found : C, 65·6; H, 4·6; Cl, 16·4. $C_{12}H_{10}ONCl$ requires C, 65·6; H, 4·6; Cl, 16·2%).

7-Chloro-2-naphthol.—The above chloro-amine (1·2 g.) was dissolved in a mixture of glacial acetic acid (7 ml.) and concentrated sulphuric acid (12 ml.) and stirred during the addition of water (60 ml.). The finely divided suspension of the amine sulphate was diazotised by dropwise addition of sodium

nitrite (0·5 g.) in water (5 ml.) at 0—10°. After 3 hours' stirring excess of nitrous acid was destroyed by urea, and the diazonium solution was decomposed by dropwise addition to boiling 2N-sulphuric acid (80 ml.). The product was extracted from the cooled solution with ether, and the extract washed with sodium hydrogen carbonate solution, dried, and freed from solvent. Extraction of the residual dark red oil with boiling light petroleum (b. p. 60—80°) (charcoal) gave 7-chloro-2-naphthol (0·55 g., 46%), m. p. 124—126°, which crystallised from the same solvent in large rhombic prisms, m. p. 126—127° (Found: Cl, 19·7. Calc. for $C_{10}H_7OCl$: Cl, 19·9%). Franzel and Deibel (*loc. cit.*) give m. p. 126·5°. The *acetate*, crystallised from methyl alcohol in stout rhombs, m. p. 105—106° (Found: C, 65·3; H, 4·2; Cl, 16·0. $C_{12}H_9O_2Cl$ requires C, 65·3; H, 4·1; Cl, 16·1%).

5-Nitro-2-naphthol.—Prepared from 5-nitro-2-naphthylamine in quantitative yield (cf. Cook *et al.*, *J.*, 1934, 653) this gave an *acetate* which crystallised from ethyl alcohol in dark yellow, stout prisms, m. p. 98—99° (Found: C, 62·1; H, 4·0. $C_{12}H_9O_4N$ requires C, 62·3; H, 3·9%), and a methyl ether, golden yellow plates (from methyl alcohol), m. p. 76—77° (Found: C, 65·2; H, 4·4. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·4%) (Cook *et al.*, *loc. cit.*, give m. p. 74·5—75·5°).

5-Amino-2-naphthol.—The above nitronaphthol (4·0 g.), shaken in alcoholic solution with Raney nickel, rapidly absorbed the theoretical amount of hydrogen. The filtered solution was concentrated and gave the amino-naphthol (2·8 g.) in colourless prisms, m. p. 183—184° (Friedlander and Szymanski, *Ber.*, 1892, **25**, 2079, give m. p. 186°). The *monoacetate*, obtained by Raney nickel reduction of 5-nitro-2-naphthyl acetate and crystallised from methyl alcohol (charcoal), had m. p. 101—102° (Found: C, 71·6; H, 5·5. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5%). The methyl ether prepared by a similar reduction of methyl 5-nitro-2-naphthyl ether crystallised from aqueous ethyl alcohol in nacreous plates, m. p. 73—74° (Found: C, 76·0; H, 6·3. Calc. for $C_{11}H_{11}ON$: C, 76·3; H, 6·3%). Cook *et al.* (*loc. cit.*) give m. p. 73—74°.

5-Chloro-2-naphthol.—A solution of 5-amino-2-naphthyl acetate (2·0 g.) in concentrated hydrochloric acid (20 ml.) was stirred at 0—5° during the dropwise addition of sodium nitrite (0·8 g.) in water (3 ml.) and for a further 2 hours. The clear solution was then stirred for 1 hour at room temperature with a solution of cuprous chloride in concentrated hydrochloric acid. Extraction with ether gave an oily product containing some free chloronaphthol. Hydrolysis by boiling for 10 minutes with dilute aqueous sodium hydroxide, followed by acidification and isolation with ether, gave a solid which crystallised from light petroleum (b. p. 60—80°) (charcoal) in rectangular prisms, m. p. 97—98° (42%) (Found: C, 67·3; H, 4·0; Cl, 19·9. Calc. for $C_{10}H_7OCl$: C, 67·2; H, 3·9; Cl, 19·9%). The *acetate* crystallised from methyl alcohol in colourless prisms, m. p. 55—56° (Found: C, 65·2; H, 4·2; Cl, 16·4. $C_{12}H_9O_2Cl$ requires C, 65·3; H, 4·1; Cl, 16·1%). Oxidation of 5-chloro-2-naphthol with alkaline potassium permanganate gave a product, isolated with ether, which crystallised from ether–light petroleum (b. p. 40—60°) in prisms, m. p. 185—187°, undepressed on admixture with an authentic specimen of 3-chlorophthalic acid.

8-Amino-2-naphthyl Acetate.—8-Nitro-2-naphthyl acetate (5 g.) from 8-nitro-2-naphthol (Friedlander and Szymanski, *loc. cit.*), in dioxan (30 ml.), was reduced by hydrogen in the presence of Raney nickel. The *ester*, isolated by filtration and concentration of the solution, crystallised from aqueous methyl alcohol in prisms, m. p. 82—83° (Found: C, 71·6; H, 5·6. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5%).

8-Chloro-2-naphthol.—This was obtained from 8-amino-2-naphthyl acetate in 36% yield by the procedure used for 5-chloro-2-naphthol, the acetyl group being lost during the Sandmeyer reaction. It crystallised from light petroleum (b. p. 60—80°) in a matte of colourless needles, m. p. 101—102° (Found: C, 67·1; H, 3·7; Cl, 20·0. Calc. for $C_{10}H_7OCl$: C, 67·2; H, 3·9; Cl, 19·9%). Dilthey *et al.* (*loc. cit.*) and Claus and Volz (*Ber.*, 1885, **18**, 3157) give 101°. The *acetate* crystallised from aqueous methyl alcohol in prisms, m. p. 70—71° (Found: C, 65·4; H, 4·3. $C_{12}H_9O_2Cl$ requires C, 65·3; H, 4·1%).

1 : 3-Dichloro-2-naphthol.—This was prepared in 90% yield by refluxing a solution of 1 : 1 : 3 : 3 : 4-pentachloro-1 : 2 : 3 : 4-tetrahydro-2-ketonaphthalene (Fries and Schimmelschmidt, *Annalen*, 1930, **484**, 297) (6·0 g.) in glacial acetic acid (30 ml.) with zinc dust (6 g.) for 0·5 hour. When the mixture was poured into water a white solid (3·8 g.) was obtained which crystallised from light petroleum (b. p. 40—60°) in aggregates of hexagonal prisms, m. p. 72—74° (Found: Cl, 33·3. Calc. for $C_{10}H_6OCl_2$: Cl, 33·3%). Fries and Schimmelschmidt (*loc. cit.*) give m. p. 78°.

1 : 3 : 4-Trichloro-2-naphthol.—A solution of 1 : 1 : 3 : 3 : 4-pentachloro-1 : 2 : 3 : 4-tetrahydro-2-ketonaphthalene (10 g.) in ethyl alcohol (35 ml.) was refluxed for 0·5 hour during the dropwise addition of a solution of stannous chloride (8 g.) in concentrated hydrochloric acid (24 ml.). Addition of water to the cooled solution gave a solid (6·8 g.) which crystallised from aqueous methyl alcohol in prisms, m. p. 160—161° (Found: Cl, 42·4. Calc. for $C_{10}H_5OCl_3$: Cl, 43·0%). Fries and Schimmelschmidt (*loc. cit.*) give m. p. 162°. The *acetate*, crystallised from methyl alcohol, had m. p. 130—131° (Found: Cl, 36·1. $C_{12}H_7O_2Cl_3$ requires Cl, 36·7%).

3 : 4-Dichloro-2-naphthol.—Attempts to prepare this naphthol by reduction of the above trichloronaphthol with a zinc–copper couple (cf. G.P. 431,165) were unsuccessful. The required product was obtained in 90% yield, however, by the following method: 1 : 3 : 4-Trichloro-2-naphthol (2 g.) was dissolved in a solution of sodium hydroxide (2·8 g., 1 mol.) in water (10 ml.) and heated with a solution of ferrous sulphate (10 g.) in water (10 ml.) at 145° for 15—17 hours. On cooling, the contents of the tube were made alkaline with a little dilute sodium hydroxide solution and filtered, and the product was isolated by extracting the acidified filtrate with ether. It crystallised from light petroleum (b. p. 60—80°) in colourless slender rectangular prisms (1·5 g.), m. p. 106—108° (Found: Cl, 33·2. Calc. for $C_{10}H_6OCl_2$: Cl, 33·3%). G.P. 431,165 gives m. p. 108°. The *acetate* crystallised from methyl alcohol in feathery prisms, m. p. 72—73° (Found: C, 56·7; H, 3·2. $C_{12}H_8O_2Cl_2$ requires C, 56·5; H, 3·1%).

2-Naphthyloxyacetic Acids.—These were prepared by the following general procedure, analytical

details being given in the Table. An ethyl-alcoholic solution of the naphthol was treated with sodium ethoxide (1 mol.), and the whole heated for 2 hours under reflux with ethyl bromoacetate (1 mol.). After the addition of excess of 10% sodium hydroxide solution the whole was heated for a further 1 hour, cooled, and acidified with concentrated hydrochloric acid. The product was isolated with ether and obtained free from naphthol by extraction with sodium hydrogen carbonate solution.

Substituted 2-naphthyloxyacetic acids.

			Found:				Required:		
Substituent	M. p.	Solvent	C, %	H, %	Cl, %	Formula	C, %	H, %	Cl, %
3-Chloro	182—183°	AcOH	60·5	4·0	15·4	$C_{12}H_9O_3Cl$	60·9	3·8	15·0
4- ,, ...	168—169	,,	60·6	4·2	14·4				
5- ,, ...	202—203	MeOH	61·0	3·6	14·5				
6- ,, ...	208—209	MeOH	61·1	3·6	15·5				
7- ,, ...	168—169	MeOH	60·8	3·8	14·7				
8- ,, ...	131—132	Et_2O–light petroleum	60·7	3·6	14·8				
1 : 3-Dichloro	179—180	aq. MeOH	53·5	3·2	25·8	$C_{12}H_8O_3Cl_2$	53·1	3·0	26·2
1 : 4- ,,	188—189	,,	53·3	3·0	25·9				
3 : 4- ,,	182—184	MeOH	53·0	3·3	25·7				
1 : 3 : 4-Trichloro	207—208	AcOH	47·3	2·4	34·7	$C_{12}H_7O_3Cl_3$	47·15	2·3	34·8
5-Nitro	211—212	EtOH	58·5	3·5	—	$C_{12}H_9O_5N$	58·3	3·6	—
8- ,, ...	179—180	aq. MeOH	58·0	3·7	—				

The authors thank Professor H. Burton for a gift of 1 : 4-dichloro-2-naphthol, and Mr. R. F. Batt for the chlorine analyses.

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[*Received, August 10th*, 1951.]

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753. *Coenzyme A. Part III.* Synthesis of Pantothenic Acid-2′ : 4′ Phosphate and Further Structural Considerations.*

By J. Baddiley and E. M. Thain.

The cyclic phosphate of pantothenic acid (II; R = R′ = H) has been synthesised by phosphorylation of benzyl pantothenate with phenyl dichlorophosphinate followed by hydrogenolysis. Its behaviour on paper chromatography before and after hydrolysis has been studied. From its inactivity in the *Acetobacter* test it is concluded that this substance is not identical with any known degradation product of coenzyme A.

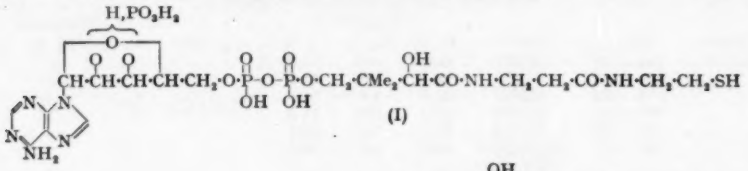
The earlier suggestion that a phosphate group is situated at 2′ or 3′ in the adenosine moiety of coenzyme A is supported by its behaviour towards periodate.

In Part II * it was shown that coenzyme A gave on mild acid or alkaline hydrolysis a substance indistinguishable on paper chromatography in two different solvent systems from pantothenic acid-4′ phosphate which had been synthesised earlier (Baddiley and Thain, *J.*, 1951, 246). A tentative formula (I) was advanced for the coenzyme. However, the inability of this synthetic phosphate to stimulate the growth of *Acetobacter suboxydans* was somewhat disturbing. It is known (Novelli, Flynn, and Lipmann, *J. Biol. Chem.*, 1949, **177**, 493) that certain enzymic fission products of coenzyme A, in which both phosphate and pantothenic acid groupings are present, exhibit activity in this test. A possible explanation was advanced at the time, namely, that activity in this test required the integrity of the 2-mercaptoethylamine residue normally present in coenzyme A. From a study of the enzymic degradation of coenzyme A, Novelli (private communication) has shown this to be incorrect, the 2-mercaptoethylamine residue not being an essential component of coenzyme fragments which show marked growth activity towards *A. suboxydans*. The 2′-phosphate and the 2′ : 4′-diphosphate of pantothenic acid were also without activity in this test and were in fact absent in coenzyme hydrolysates. There remained the possibility that a cyclic phosphate structure might be present in the coenzyme.

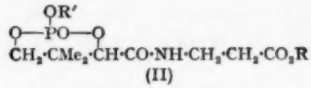
* Part II, *J.*, 1951, 2253.

Pantothenic acid-2′ : 4′ phosphate (II; R = R′ = H) was hitherto unknown and its behaviour on paper before and after hydrolysis could not be predicted. This cyclic phosphate has now been prepared and its stability towards acids and alkalis examined.

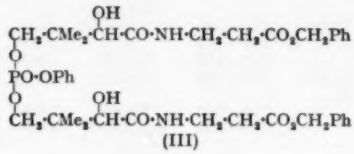
Benzyl pantothenate was phosphorylated with phenyl dichlorophosphinate in pyridine giving a syrupy product, presumably (II; R = Ph·CH_2, R′ = Ph). The formation of products



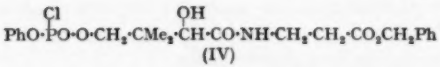
(I)



(II)



(III)



(IV)

from reaction between one molecule of phenyl dichlorophosphinate and two molecules of benzyl pantothenate, *e.g.*, (III) and its isomers, was prevented by effecting phosphorylation in dilute solution. The probable intermediate in this reaction, (IV) may react further in two possible ways. With a second molecule of benzyl pantothenate it would give (III) or an isomer in which the phosphate linkage involves the 2′-hydroxyl group. Cyclisation on the other hand would give (II; R = Ph·CH_2, R′ = Ph). The latter reaction, unlike the former, should be independent of concentration and so more likely to predominate in dilute solution. The syrupy product was hydrogenated with a palladium catalyst to remove the benzyl group, and the phenyl group was removed more slowly by hydrogenolysis with a platinum catalyst in acetic acid. Pantothenic acid-2′-: 4′-phosphate (II; R = R′ = H) was isolated as its barium salt and purified through its strychnine and brucine salts. Analysis of the reaction mixture before isolation showed that only traces of phosphorylated by-products were present.

Paper chromatography provided a ready means of distinguishing between the cyclic phosphate and other phosphates of pantothenic acid. In *n*-propyl alcohol–ammonia and in *iso*butyric acid–ammonium *iso*butyrate–water it moved more rapidly than the other phosphates.

It is clear then that the substance obtained from hydrolysis of coenzyme A is not pantothenic acid-2′ : 4′ phosphate. The possibility that the coenzyme might contain a similar cyclic structure was not ruled out by this observation, however, since such a phosphate ring may have been opened during hydrolysis. In support of this argument it was shown that the 2′ : 4′-phosphate was hydrolysed very readily in alkali. Hydrolysis was complete after one hour at 100° in 0·35N-barium hydroxide solution, conditions similar to those employed in the hydrolysis of coenzyme A. The product was shown by paper chromatography to be pantothenic acid-4′ phosphate. No trace of the 2′-phosphate could be detected. The cyclic phosphate was largely unchanged by N-sulphuric acid at 100° during 20 minutes. Novelli has shown that coenzyme A hydrolysates retain their activity in the *Acetobacter* test after such treatment. Although these observations are consistent with the formulation of the coenzyme as a derivative of pantothenic acid-2′ : 4′ phosphate such a structure cannot be correct since the (±)-cyclic phosphate was quite inactive in stimulating the growth of *A. suboxydans*. Furthermore, it was not hydrolysed by acid or alkali phosphatase whereas the active fragments from coenzyme A were readily dephosphorylated by such treatment.

Forrest and Todd (*J.*, 1950, 3295) observed the formation of a cyclic phosphate of riboflavin during the hydrolysis of flavin–adenine dinucleotide with ammonia. Similarly, the isomerisation of adenosine phosphates during acid hydrolysis probably occurs through cyclic intermediates (Brown, Haynes, and Todd, *ibid.*, p. 2299). In the pantothenic acid phosphates neither cyclisation nor the formation of isomers during hydrolysis has been observed so far.

In view of the inability of all the synthetic pantothenic acid phosphates to stimulate the

growth of *A. suboxydans* it would seem likely that coenzyme A bears an as yet unidentified residue attached to the pantothenic acid moiety. On the basis of present evidence it is not possible to state whether this group is situated at the 2′-position in a pantothenic acid-4′ phosphate structure or whether it is interposed between phosphate and pantothenic acid. However, we have shown that the phosphate group in adenosine-5′ phosphate and adenylic acids a and b are hydrolysed completely in 24 hours at 100° in 0·5N-alkali whereas the substance obtained by alkali hydrolysis of coenzyme A, like pantothenic acid-4′ phosphate, is quite stable under these conditions. This relative lability of derivatives of ribose phosphate suggests that if the unidentified residue in coenzyme A is interposed between the pyrophosphate linkage and pantothenic acid then it is most unlikely to be ribose.

It is now established that coenzyme A contains three phosphate groups (Novelli, Gregory, Flynn, and Schnetz, *Fed. Proc.*, 1951, **10**, 229). Two of these are very probably involved in pyrophosphate linkages as shown in (I) while the third, which from enzyme experiments appears to be bound as a monoester, has been assigned provisionally to either position 2′ or 3′ in the adenosine residue (cf. Part II, *loc. cit.*). Further evidence in support of this view has been forthcoming from a study of the behaviour of coenzyme A towards periodate. The method of Buchanan, Dekker, and Long (*J.*, 1950, 3162) was employed. In this method the nucleotide is oxidised on filter paper with a solution of sodium metaperiodate and resulting dialdehydes detected by spraying with Schiff's reagent. Nucleotides substituted at position 2′ or 3′ give no dialdehydes while those unsubstituted in these positions are oxidised readily under these conditions. Coenzyme A gave no dialdehyde when oxidised in this way whereas after hydrolysis in acid and oxidation under identical conditions dialdehydes were detected quite readily. Control experiments on proportionate amounts of adenosine-5′ phosphate and adenylic acids a and b confirmed that the observations had been made well within the limits of sensitivity of the method. It follows then that the coenzyme bears a substituent, presumably a monophosphate, at position 2′ or 3′ in the adenosine residue. At the present time no method exists for distinguishing between positions 2′ and 3′ in the adenine nucleotides.

Experimental.

D-*Pantothenic Acid-2′ : 4′ Phosphate* (II; R = R′ = H).—Benzyl pantothenate (14·8 g.) (Kuhn and Wieland, *Ber.*, 1940, **73**, 971) prepared from D(−)-pantolactone was dissolved in anhydrous pyridine (600 c.c.), and the solution cooled in a bath of acetone–solid carbon dioxide until the pyridine started to crystallise. A cold solution of phenyl dichlorophosphinate (10·6 g.) (Brigl and Müller, *ibid.*, 1939, **72**, 2121) in a little anhydrous pyridine was added in one lot. The solution was kept in the cooling-bath during 10 minutes, then allowed to reach room temperature. Reaction was completed by heating at 60—70° for 4 hours, then storage overnight. Most of the pyridine was removed by evaporation under reduced pressure and the remaining reddish-brown syrup dissolved in chloroform, washed with water, cold N-sulphuric acid, sodium hydrogen carbonate solution, and finally water. Chloroform was removed by evaporation under reduced pressure, and the residue dissolved in alcohol, decolorised with charcoal, and evaporated, to a pale amber resin (15·5 g.). A solution of this in 80% alcohol was hydrogenated at room temperature and atmospheric pressure in the presence of hydrogen and a palladium oxide catalyst. Hydrogen was absorbed quite rapidly until the benzyl group had been removed, then absorption ceased abruptly. Catalyst was removed by filtration, and solvent evaporated under reduced pressure. The resulting colourless resin was dissolved in chloroform, washed twice with water, and freed from solvent. The resin was dissolved in acetic acid, and the phenyl group removed by hydrogenolysis at room temperature and atmospheric pressure with hydrogen and a platinum oxide catalyst. Reduction was slow unless a relatively large amount of catalyst was used. Catalyst was removed by filtration and a solution of barium acetate (11 g.) in water (25 c.c.) added. Solvent was removed by evaporation under reduced pressure and most of the acetic acid by evaporation twice with water. The residue was dissolved in water, adjusted to pH 8 with barium hydroxide solution, and diluted with 2 volumes of alcohol. The small precipitate was removed by centrifugation and the clear supernatant liquid evaporated to small volume. Impure barium salt (10 g.) was obtained by addition of a large volume of acetone and collection of the insoluble salt by centrifugation. This salt was dissolved in a little water and passed through a column of Amberlite I.R. 120 (H), to remove barium ions. The eluate was evaporated to dryness from the frozen state, to remove water and acetic acid, and the residue dissolved in water and adjusted to pH 8 with barium hydroxide solution. After evaporation to small volume under reduced pressure the barium salt was precipitated by addition of a large volume of acetone. The product was washed well with acetone and dried over phosphoric oxide.

Preparation of strychnine salt. The barium salt of pantothenic acid-2′ : 4′ phosphate (2·5 g.) was freed from barium by quantitative precipitation with sulphuric acid, barium sulphate removed by centrifugation, strychnine (4 g., 2 mols.) added to the clear solution, and the mixture warmed to effect dissolution. The crystalline solid remaining on evaporation of the water was recrystallised from a small volume of hot water to which acetone was added to incipient opalescence. The strychnine salt crystallised as tiny plates, m. p. 175—177° (decomp.). Analyses indicated that this material was a mixture of the mono- and di-strychnine salts (Found: C, 60·8; H, 6·6; N, 7·0; P, 3·2. Calc. for $C_{51}H_{56}O_{11}N_4P$: C, 64·6; H, 6·3; N, 7·4; P, 3·3. Calc. for $C_{36}H_{41}O_9N_3P$: C, 58·5; H, 6·2; N, 6·8; P, 5·0%). Attempts to prepare the monostrychnine salt only yielded uncrystallisable resins.

Reconversion of the strychnine salt into the barium salt. The foregoing strychnine salt (4 g.) was dissolved in water (*ca.* 5 c.c.), and barium hydroxide solution (0·3N) added to pH 9. Carbon dioxide was passed through the solution to remove excess barium hydroxide, and the strychnine and barium carbonate were removed by filtration. The filtrate was concentrated under reduced pressure and the *barium* salt (1·5 g.; theory, 1·75 g.) precipitated by the addition of excess acetone [Found, in substance dried at 140°: Ba, 31·7; P, 7·4; N(Kjeldahl), 3·1. $C_9H_{14}O_7NPBa,H_2O$ requires Ba, 31·7; P, 7·2; N, 3·2%]. $[\alpha]_{44}^{D}$ +29° (*c*, 2·12 in. water).

Preparation of the brucine salt. The barium salt (0·8 g.) was freed from barium by sulphuric acid as before, and brucine (1·6 g., 2 mols.) added to the aqueous solution of the free acid. The solid remaining on evaporation of the water was crystallised by dissolving it in the minimum of hot water and adding acetone to incipient opalescence. The *brucine* salt crystallised as well-formed, rectangular prisms (1·65 g., 80%), m. p. 135° with effervescence; after drying in a vacuum at 100° it had m. p. *ca.* 165° (to a resinous material) (Found: C, 54·5; H, 7·0; N, 6·0; P, 2·7; loss on drying at 140°, 12·0. $C_{44}H_{68}O_{13}N_4P,8H_2O$ requires C, 54·5; H, 6·9; N, 5·8; P, 2·6; H_2O, 11·9%).

Hydrolysis of Pantothenic Acid-2′ : 4′ Phosphate.—(a) *Alkali.* The barium salt (1 mg.) of the cyclic phosphate was heated with barium hydroxide solution (0·25 c.c.; 0·3N) at 100° for 1·5 hours in a sealed tube. Barium hydroxide was precipitated by carbon dioxide as barium carbonate which was removed by centrifugation. The barium from soluble barium salts was removed by addition of ammonium sulphate. After removal of barium sulphate the solution was concentrated and run on paper using *n*-propyl alcohol–ammonia–water as solvent. The chromatogram was developed by Hanes and Isherwood's molybdate spray (*Nature*, 1949, **164**, 1107). It was found that pantothenic acid-2′ : 4′ phosphate, R_F 0·62, was converted entirely into pantothenic acid-4′ phosphate, R_F 0·32, by this hydrolysis.

(b) *Acid.* The barium salt (1 mg.) of the cyclic phosphate, dissolved in 1 drop of water, was heated with sulphuric acid (0·25 c.c.; N) at 100° for 20 minutes in a sealed tube. The cooled solution was neutralised with barium hydroxide, and the precipitate of barium sulphate removed by centrifugation. Barium was removed from soluble barium salts as before, and after removal of barium sulphate the solution was run on paper with *n*-propyl alcohol–ammonia–water. The acid-treated material gave a spot identical with that of the cyclic phosphate; no trace of either pantothenic acid-2′ or -4′ phosphate was visible.

Prolonged Alkaline Hydrolysis of Coenzyme A, Pantothenic Acid-4′ Phosphate, and Adenosine Phosphates.—Two samples each of coenzyme A (1·5 mg.; 170 units/mg.), the barium salt of pantothenic acid-4′ phosphate (1 mg.), adenosine-5′ phosphate (1 mg.), and commercial yeast adenylic acid (1 mg.) were separately dissolved in barium hydroxide solution (0·5 c.c.; 0·3N) and sealed in glass tubes. One series of tubes was heated at 100° for 45 minutes, the other at 100° for 24 hours. The contents were treated in the usual way for the removal of barium, and the residues run on paper in *n*-propyl alcohol–ammonia–water and *iso*butyric acid–ammonium *iso*butyrate–water. In both solvent systems the two adenosine phosphates were mainly hydrolysed after 45 minutes and completely after 24 hours. Coenzyme A after 45 minutes' hydrolysis and running in *n*-propyl alcohol–ammmonia–water gave 4 spots, the slowest-moving of which corresponded to pantothenic acid-4′ phosphate (R_F 0·36), the faster-moving spots having R_F 0·60, 0·68, and 0·76; in *iso*butyric acid–ammonium *iso*butyrate only one spot was observed, having an R_F, 0·47, which is slightly faster than pantothenic acid-4′ phosphate, R_F 0·43. In both solvent systems the hydrolysate after 24 hours gave one spot only, corresponding to pantothenic acid-4′ phosphate, which is stable to these conditions of hydrolysis.

Action of Sodium Metaperiodate on Coenzyme A.—Coenzyme A (1 mg.; 330 units/mg.) was dissolved in water (0·02 c.c.), and the solution divided into two parts. One part was hydrolysed with hydrochloric acid (0·05 c.c.; N) for 1 hour at 100° and then evaporated. Adenylic acid b (50 mg.) was similarly treated. Parts of the resulting solutions were put on paper, and the chromatogram developed with *n*-propyl alcohol–ammonia–water; the remaining parts were spotted out on paper and treated with sodium metaperiodate solution directly, according to the method of Buchanan, Dekker, and Long (*loc. cit.*). The paper which was treated directly showed that unhydrolysed coenzyme A and adenylic acid b gave no reaction, whereas both after hydrolysis gave positive reactions for aldehyde. A similar result was obtained with the developed chromatogram. Coenzyme A, which gave 5 spots when examined in ultra-violet light, gave no Schiff's reaction whilst both coenzyme A and adenylic acid b after hydrolysis gave strong Schiff-reacting spots at identical positions on the paper.

Sincere thanks are offered, with respect to this and the following paper, to Drs. F. Lipmann, G. D. Novelli and their collaborators for friendly co-operation both in discussion, in performing the growth tests on *A. suboxydans*, and for the gift of samples of coenzyme A. Thanks are also offered to Roche Products Ltd. and Imperial Chemical Industries Limited, Dyestuffs Division, for gifts of chemicals and the Department of Scientific and Industrial Research for a Special Research Grant.

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[*Received, August 17th*, 1951.]

754. *Coenzyme A. Part IV.* Derivatives of 2-Acetylthioethylamine as Acetylating Agents.*

By J. Baddiley and E. M. Thain.

2-Acetylthioethylamine hydrochloride, *N*-2′-acetylthioethylacetamide (2-acetamidoethyl thiolacetate) (I), and the acetylated dipeptide (II) have been synthesised and their capacity to acetylate hydroxylamine in aqueous solution at room temperature has been investigated. All three substances reacted almost instantaneously under these conditions giving *N*-acetylhydroxylamine and the corresponding thiols. These experiments, which demonstrate the very reactive nature of the thiolacetate group in such substances, support the suggestion by Lynen and Reichert (*Angew. Chem.*, 1951, **63**, 47) that coenzyme A functions as an acetylating coenzyme in Nature by acetyl transfer at its terminal thiol group.

It was shown by Lynen and Reichert (*Angew. Chem.*, 1951, **63**, 47) that during enzymic acetylations involving coenzyme A an intermediate is formed in which the thiol group in the coenzyme is substituted, probably being present as a thiolacetate. The thiolacetate then transfers its acetyl group to the substrate. As a basis for the further study of these reactions a preliminary investigation of certain properties of related thiols seemed desirable. The terminal thiol group in coenzyme A is part of a 2-mercaptoethylamine residue in which the amino-group is involved in amide linkage with a substituted pantothenic acid (Snell, Brown, Peters, Craig, Wittle, Moore, McGlohon, and Bird, *J. Amer. Chem. Soc.*, 1950, **72**, 5349; Baddiley and Thain, *J.*, 1951, 2253). The chemistry of thiolacetates, particularly those derived from 2-mercaptoethylamine derivatives, has received little attention hitherto and in this paper we describe the preparation of some compounds of this type and their behaviour towards hydroxylamine.

2-Acetylthioethylamine hydrochloride was prepared readily by treatment of 2-mercaptoethylamine hydrochloride with an excess of acetyl chloride The amino-group was not acetylated under these conditions. A closer analogy to coenzyme A, however, is to be found in 2′-acetylthioacetamide (2′-acetamidoethyl thiolacetate) (I) where the basicity of the amino-group has been reduced by acetylation. This was formed by reaction of 2-mercaptoethylamine with acetic anhydride in pyridine. The acetylated dipeptide (II) possesses several features in common with coenzyme A. Besides the thiolacetate residue it contains the β-alanine amide structure and differs from the coenzyme only in that in place of the phosphorylated pantoic moiety an acetyl group has been substituted. It was prepared by treating acetyl-β-alanine methyl ester with 2-mercaptoethylamine and acetylating the resulting thiol with acetic anhydride. The free thiol was unstable in air, readily giving rise to the disulphide (III).

(I) Me·CO·NH·CH_2·CH_2·S·COMe (Me·CO·NH·CH_2·CH_2·CO·NH·CH_2·CH_2·S)$_2$ (III)

(II) Me·CO·NH·CH_2·CH_2·CO·NH·CH_2·CH_2·S·COMe

2-Acetylthioethylamine hydrochloride was very unstable in aqueous solution. A fresh solution gave a negative reaction for thiol as determined by its stability towards an iodine solution. After the solution had been kept at room temperature for a few minutes, however, a strong positive thiol test was obtained, indicating fission of the thiolacetate bond. In neutral solution decomposition was also very rapid. The nature of the reaction products was not determined but it seems probable that two competing reactions were involved, namely, (i) hydrolysis to acetic acid and 2-mercaptoethylamine and (ii) transfer of the acetyl group from sulphur to nitrogen. The second reaction would tend to predominate in neutral or alkaline solution while the simple hydrolysis would occur mainly in acids. The amide (I) and the peptide (II), in both of which the basicity of the amino-group had been reduced by acetylation, were quite stable in neutral solution.

The three substances were examined by Dr. Lipmann as acetylating agents. He reports that all three reacted almost instantaneously with hydroxylamine in aqueous solution at room temperature, effecting *N*-acetylation. A little difficulty was experienced with 2-acetylthioethylamine hydrochloride in view of its instability in solution and for this reason acetylation by this substance was never quantitative. We have shown that (I) and (II) react readily with ammonia in aqueous solution at room temperature, liberating thiols.

* Part III, preceding paper.

These results indicate that certain thiolacetates, in particular those derived from 2-mercaptoethylamides, are effective acetylating agents and in this respect support the suggestion by Lynen and Reichert (*loc. cit.*) that coenzyme A brings about acetylation by acetyl transfer through its thiol group. Whether the final step in the biological acetylation process, namely, the transfer of acetyl from acetyl-coenzyme A to the substrate, is a non-enzymic (*i.e.*, spontaneous) reaction is not known.

The origin of the 2-mercaptoethylamine residue in the coenzyme is uncertain, but it would seem likely that it is derived from cysteine through decarboxylation. It is of interest that the neighbouring residue in coenzyme A, β-alanine, may have originated in a similar manner by decarboxylation of aspartic acid. While no evidence is available in connection with the first suggestion it has been shown that aspartic acid can be decarboxylated to β-alanine by certain bacteria (Ackermann, *Z. physiol. Chem.* 1907, **54**, 1; 1909, **60**, 482; Virtanen and Laine, *Enzymologia*, 1937, **3**, 266; Virtanen, Rintala, and Laine, *Nature*, 1938, **142**, 674). It appears that β-alanine is incorporated *per se* into pantothenic acid, and hence into coenzyme A, since pantoylaspartate is without activity as a substitute for pantothenic acid (Weinstock, May, Arnold, and Price, *J. Biol. Chem.*, 1940, **135**, 343). Whether 2-mercaptoethylamine is also incorporated *per se* into the coenzyme, or whether pantothenylcysteine could be utilised, is of considerable interest. In this connection and in other studies on biological precursors of coenzyme A the peptide (II) may provide a useful model.

Experimental.

2-Acetylthioethylamine Hydrochloride (*2-Aminoethyl Thiolacetate Hydrochloride*).—Finely powdered anhydrous 2-mercaptoethylamine hydrochloride (10 g.) was suspended in acetyl chloride (50 c.c.), and the mixture warmed gently. When evolution of hydrogen chloride had ceased the crystalline solid was removed by filtration, washed with ether, and recrystallised from alcohol (yield 7 g.). *2-Acetylthioethylamine hydrochloride* formed prisms, m. p. 146—147° (Found: C, 30·9; H, 6·2; N, 8·8; S, 20·6; Cl, 22·8. $C_4H_{10}ONSCl$ requires C, 30·9; H, 6·4; N, 9·0; S, 20·5; Cl, 22·8%).

2′-Acetylthioethylacetamide (*2-Acetamidoethyl Thiolacetate*).—Acetic anhydride (10·5 c.c.) was added to a solution of 2-mercaptoethylamine (3 g.) in anhydrous pyridine (40 c.c.). Heat was evolved during the initial stages of the reaction. Next morning methanol (10 c.c.) was added and the solution kept at room temperature for 30 minutes to permit decomposition of the excess of acetic anhydride. Solvent was removed by evaporation under reduced pressure and pyridine acetate removed by heating at 100°/*ca.* 0·1 mm. The syrupy residue was distilled under high vacuum. The main fraction (4 g.) was collected at 100°/10^{-5} mm. and crystallised in the receiver. *2′-Acetylthioethylacetamide* crystallised as long needles, m. p. 26—28° (Found: C, 44·2; H, 7·0; N, 8·6. $C_6H_{11}O_2NS$ requires C, 44·5; H, 6·8; N, 8·7%).

N-Acetyl-β-alanine Methyl Ester.—Dry, finely powdered β-alanine (8 g.) was added to acetic anhydride (25 c.c.), and the mixture heated at 100° for about 10 minutes, during which all solid had dissolved. Most of the acetic anhydride and acetic acid was removed by distillation under reduced pressure on a steam-bath and last traces of anhydride were decomposed by addition of water, then evaporation under reduced pressure. Sodium hydroxide (60 ml.; 2N) was added and after 30 minutes at room temperature sulphuric acid (2N) was added exactly equivalent to the alkali used. The solution was evaporated to dryness in a vacuum and the acetyl compound extracted from the residue with warm alcohol (100 c.c.). The filtered alcoholic solution was evaporated to dryness, leaving a clear syrup which did not crystallise. This was dissolved in methyl alcohol, then cooled to 5°, and an excess of ethereal diazomethane added. Solvents were removed by evaporation under reduced pressure and the remaining syrup distilled. After discarding of a small fraction boiling below 100°/0·6 mm., *acetyl-β-alanine methyl ester* was collected at 110—112°/0·6 mm., crystallising in the receiver, m. p. 20—25° (4·5 g.) (Found: C, 49·2; H, 7·7. $C_6H_{11}O_3N$ requires C, 49·6; H, 7·6%).

SN-*Diacetyl-β-alanyl-2-mercaptoethylamine* [*β-Acetamido-*N*-(2-acetylthioethyl)propionamide*] (II).—A mixture of 2-mercaptoethylamine (2 g.) and acetyl-β-alanine methyl ester (1·1 g.) was heated for 8 hours in an atmosphere of coal gas at 100°. The reaction mixture solidified on cooling. The product, which consisted largely of the monoacetyl dipeptide, melted at about 110° but was not characterised further since it oxidised readily in air to the disulphide (III). After being washed with ether it was heated for 1 hour on a steam-bath with acetic anhydride (about 20 c.c.). The reaction mixture was evaporated to a syrup under reduced pressure, the residue kept in methyl alcohol for 30 minutes, evaporated to dryness, and extracted with hot ethyl acetate. The insoluble part consisted of *di-*[*2-(β-acetamidopropionamido)ethyl*] *disulphide* (III), m. p. 190° (Found: C, 44·7; H, 7·1; N, 14·9; S, 17·3. $C_{14}H_{26}O_4N_4S_2$ requires C, 44·4; H, 6·9; N, 14·9; S, 16·9%). The ethyl acetate solution was evaporated to small volume and cooled. The *acetyl dipeptide* (II) crystallised out as rosettes, m. p. 131—132°, after recrystallisation from ethyl acetate (Found: C, 46·6; H, 7·2; N, 11·7; S, 13·7. $C_9H_{16}O_3N_2S$ requires C, 46·6; H, 6·9; N, 12·0; S, 13·8%).

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[*Received, August 17th*, 1951.]

755. *Purpurogallin. Part IX.* The Structure of the Isomeric O-Methyl Ethers of β-Methyltropolone.*

By Philip Akroyd, Robert D. Haworth, and John D. Hobson.

The methoxyl group of β-methyltropolone methyl ether-A or -B is readily replaced by the amino-, anilino-, or hydrazino-group, and the properties of these derivatives are described. The Stevens–McFadyen decomposition reaction has been applied to the hydrazino-derivatives-A and -B, and the products have been reduced to 3- and 4-methyl*cyclo*heptanone, respectively. Consequently the -A and the -B series are assigned structures (I) and (II), respectively.

In Part IV of this series (*J.*, 1951, 561) attention was drawn to the existence of isomeric forms of the *O*-acyl and the *O*-alkyl derivatives of a number of tropolones. Two β-methyltropolone methyl ethers, m. p. 97° and m. p. 46°, were described and referred to as the methyl ethers -A and -B, respectively, the suffix A being ascribed arbitrarily to the higher-melting and less soluble ether until methods for determining the structure were developed.

Fernholz (*Chem. Ber.*, 1951, **84**, 110) observed that benzene or chloroform solutions of perbenzoic acid oxidised the aromatic nucleus of certain phenolic ethers, including the dimethoxy- and trimethoxy-compounds colchicine and colchiceine; the reactions have usually been followed by uptake of per-acid, but the products of the reaction were rarely determined. It was thought that perbenzoic acid might attack *O*-tetramethylpurpurogallin with the formation of a derivative of tropolone of known structure, but preliminary experiments showed that tropolone derivatives were not produced, and the reaction was not investigated further.

Although it has not been possible to replace the hydroxyl group of β-methyltropolone by chlorine, it was observed that β-methyltropolone methyl ethers-A and -B reacted with ammonia in sealed tubes to give the 2-aminomethyl*cyclo*heptatrienones-A and -B, m. p. 112° and 123°, respectively; during the course of these experiments Doering and Knox (*J. Amer. Chem. Soc.*, 1951, **73**, 828) have described the preparation of 2-amino*cyclo*heptatrienone from tropolone methyl ether. The reaction resembles the conversion of esters into amides and the products, like amides, were readily hydrolysed to β-methyltropolone by warming them with alkalis. The 2-amino-methyl*cyclo*heptatrienones formed *N*-acetyl derivatives, and stable hydrochlorides and sulphates, and a bright red azo-dye was precipitated when *p*-chlorobenzenediazonium chloride was added to alkaline solutions of the amino-tropones. The amino-methyl*cyclo*heptatrienones reacted vigorously with nitrous acid at 0° without the formation of diazonium compounds; the nature of the products is under investigation. The 2-anilino-methyl*cyclo*heptatrienones-A and -B, m. p. 121° and m. p. 99°, respectively, were obtained either by heating the corresponding methyl ethers with methanolic aniline at 90°, or by refluxing the corresponding 2-amino-methyl*cyclo*heptatrienones with aniline. The methoxyl group of β-methyltropolone methyl ethers-A and -B may also be replaced by the hydrazino-grouping yielding the crystalline 2-hydrazino-methyl*cyclo*heptatrienones-A and -B, m. p. 124° and m. p. 135° respectively; the former was converted by the action of nitrous acid into 2-amino-methyl*cyclo*heptatrienone-A, m. p. 112°, described above. The 2-hydrazino-methyl*cyclo*heptatrienones-A and -B gave crystalline benzenesulphonyl derivatives, m. p. 199° and m. p. 188°, respectively, which, in the presence of sodium carbonate, undergo the Stevens–McFadyen (*J.*, 1936, 584) decomposition, and yield 3- and 4-methyl*cyclo*heptatrienone, respectively. These non-ketonic, basic substances (compare Dauben and Ringold; Doering and Detert, *J. Amer. Chem. Soc.*, 1951, **73**, 876) were oils, which gave, on catalytic reduction, 3- and 4-methyl*cyclo*heptanone, respectively (Adamson and Kenner, *J.*, 1939, 181), which were identified by comparison of the semicarbazones, m. p. 179—180° and m. p. 158—160°, respectively, with authentic samples kindly supplied by Mlle. Tchoubar (Tchoubar, *Bull. Soc. chim.*, 1949, **16**, 164). It follows from the above series of reactions that β-methyltropolone methyl ethers-A and -B are 2-methoxy-6- (I; R = OMe) and 2-methoxy-4-methyl*cyclo*heptatrienone (II; R = OMe), respectively, and dipole-moments measurements of the two methyl ethers, made by Dr. L. E. Sutton and Mr. M. F. Saxby at Oxford (personal communication from Dr. Sutton), support the constitutions now advanced. The structures of 2-amino- and 2-anilino-methyl*cyclo*heptatrienones-*A*,

* Part VIII, *J.*, 1951, 2067.

prepared from (I; R = OMe), are therefore fixed as (I; R = NH_2) and (I; R = NHPh), and those of the B-isomers, prepared from (II; R = OMe), as (II; R = NH_2) and (II; R = NHPh), respectively.

(I) (II)

The reactions mentioned above are fully consistent with the representation of the tropolone structure as a trivinyl analogue of a carboxylic acid, but the structures now assigned to the two methyl ethers of β-methyltropolone do not give a very ready explanation of the comparatively easy oxidation to the corresponding aldehyde (see Part IV, *loc. cit.*) or of the hygroscopic nature of the ether (II; R = OMe). The former may be related to the greater hyperconjugation associated with the extended conjugation of (II; R = OMe).

Experimental.

2-*Amino*-6-*methyl*cyclo*heptatrienone* (I; R = NH_2).—2-Methoxy-6-methyl*cyclo*heptatrienone (I; R = OMe) (0·6 g., m. p. 96—97°) and methyl alcohol (5 c.c.), saturated with ammonia at room temperature, were heated in a sealed tube for 65 hours at 80°. The dark red solution was evaporated and the residue crystallised from water (charcoal) or *cyclo*hexane; pale brown elongated prisms (0·4 g.), m. p. 111—112° (Found: C, 71·2; H, 6·9; N, 10·3. C_8H_9ON requires C, 71·1; H, 6·7; N, 10·4%), readily soluble in alcohol, moderately so in ether, and insoluble in light petroleum (b. p. 40—60°), were obtained, which gave a dark green ferric test in ethyl alcohol. The *amine* (I; R = NH_2) was hydrolysed to β-methyltropolone by boiling it with 6N-sodium hydroxide solution (50 parts) for 20 hours.

p-Chlorobenzenediazonium chloride, prepared from *p*-chloroaniline (0·1 g.), N-hydrochloric acid (2 c.c.), and sodium nitrite (0·05 g.) in water (0·5 c.c.), was added to a suspension of the amine (I; R = NH_2) (0·1 g.) in 1·5N-sodium hydroxide (9 c.c.); after 6 hours the bright red precipitate was collected, suspended in water and acidified with dilute hydrochloric acid. The red azo dye was collected, dried, and crystallised from *cyclo*hexane. The *hydrochloride* separated from concentrated hydrochloric acid in elongated prisms, m. p. 248° (decomp.) (Found: N, 8·3. $C_{14}H_{19}ONCl$ requires N, 8·1%). The *sulphate* crystallised from 40% sulphuric acid in small prisms, m. p. 204° (Found: N, 6·2. $C_{14}H_{11}O_5NS$ requires N, 6·0%. The *picrate*, prepared in aqueous solution, crystallised from aqueous ethyl alcohol in yellow elongated prisms, m. p. 197—198° (decomp.) (Found: C, 46·1; H, 3·5; N, 15·6. $C_8H_9ON,C_6H_3O_7N_3$ requires C, 46·2; H, 3·3; N, 15·4%).

2-*Acetamido*-6-*methyl*cyclo*heptatrienone* (I; R = NHAc), prepared by warming the amine (I; R = NH_2) with acetic anhydride at 100° for 40 minutes, crystallised from water in elongated prisms, m. p. 115—116° (Found: C, 68·1; H, 6·4; N, 7·9. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%). Hydrolysis to the amine (I; R = NH_2) was brought about by refluxing it for 20 minutes with 70% sulphuric acid (20 parts).

2-*Amino*-4-*methyl*cyclo*heptatrienone* (II; R = NH_2).—This *compound* prepared as described above in the case of the isomer, separated from water or *cyclo*hexane in light brown prisms, m. p. 123° (Found: C, 70·9; H, 6·9; N, 10·5%), which gave a dark green ferric test. Hydrolysis to β-methyltropolone was effected by heating it with 6N-sodium hydroxide. The *hydrochloride*, separated from concentrated hydrochloric acid in long prisms, m. p. 241° (decomp.) (Found: N, 8·2%), and the *picrate* crystallised from aqueous ethyl alcohol in yellow elongated prisms, m. p. 172—173° (decomp.) (Found: C, 46·0; H, 3·4%).

2-*Acetamido*-4-*methyl*cyclo*heptatrienone* (II; R = NHAc) crystallised from *cyclo*hexane in elongated prisms, m. p. 114—115° (Found: C, 67·9; H, 6·5; N, 8·0%).

2-*Anilino*-6-*methyl*cyclo*heptatrienone* (I; R = NHPh).—This was prepared from 2-amino-6-methyl-*cyclo*heptatrienone (*a*) by refluxing it with aniline (20 parts) for 2 days or (*b*) by heating (I; R = OMe) with aniline (1·5 parts) and methyl alcohol (10 volumes) for 70 hours in a sealed tube at 80°; the *anilino*-compound crystallised from methyl alcohol in yellow elongated prisms, m. p. 121—122° (Found: C, 79·6; H, 6·3; N, 6·4. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2; N, 6·6%).

2-*Anilino*-4-*methyl*cyclo*heptatrienone* (II; R = NHPh).—When prepared as in method (*b*) described above, this *anilino*-compound separated from methyl alcohol or *cyclo*hexane in yellow elongated prisms, m. p. 98—99° (Found: C, 79·5; H, 6·3; N, 6·5%).

2-*Hydrazino*-6-*methyl*cyclo*heptatrienone* (I; R = NH·NH_2).—To a solution of 2-methoxy-6-methyl-*cyclo*heptatrienone (I; R = OMe) (2 g.) in water (2 c.c.) was added 90% hydrazine hydrate (1·5 g.), and the mixture was warmed on the water-bath for 5 minutes. After cooling, the yellow crystalline precipitate was collected, and gave, after two crystallisations from water, 2-*hydrazino*-6-*methyl*cyclo*heptatrienone* (I; R = NH·NH_2) as yellow needles (1·5 g.), m. p. 124° (Found: C, 63·7; H, 6·6; N, 18·6. $C_8H_{10}ON_2$ requires C, 64·0; H, 6·7; N, 18·6%). Dilution of the aqueous mother-liquors with water and extraction with ether yielded a further quantity (0·6 g.) of the hydrazide. The *benzylidene* derivative of (I; R = NH·NH_2) was prepared by warming (I; R = NH·NH_2) with excess of benzaldehyde; the mixture was cooled and diluted with light petroleum (b. p. 60—80°), and the yellow solid

was collected and crystallised from ethanol, giving yellow needles, m. p. 186° (Found: C, 75·4; H, 6·0; N, 11·9. $C_{13}H_{14}ON_2$ requires C, 75·6; H, 6·0; N, 11·8%). The *benzenesulphonyl* derivative (I; R = NH·NH·SO_2Ph) was obtained when benzenesulphonyl chloride (1·9 c.c.) was added slowly to a well-stirred solution of the hydrazino-derivative (I; R = NH·NH_2) (2·2 g.) in pyridine (30 c.c.), cooled in an ice-salt bath. After ½ hour, the solution was poured into a mixture of ice (100 g.) and concentrated hydrochloric acid (40 c.c.), and the resulting orange solid was collected and washed with a small quantity of dilute hydrochloric acid, and then with water. Several crystallisations from alcohol (charcoal) gave pale buff-coloured needles, m. p. 199° (decomp.), of the benzenesulphonyl derivative (I; R = NH·NH·SO_2Ph) (2·8 g.) (Found: C, 58·2; H, 5·0; N, 9·6. $C_{14}H_{14}O_2N_2S$ requires C, 57·9; H, 4·9; N, 9·7%).

2-*Hydrazino*-4-*methyl*cyclo*heptatrienone* (II; R = NH·NH_2).—When prepared in a similar manner from 2-methoxy-4-methyl*cyclo*heptatrienone (II; R = OMe) the *hydrazino*-compound (II; R = NH·NH_2) crystallised from water in yellow needles, m. p. 134—135° (Found: C, 64·3; H, 6·9; N, 18·6%). The *benzenesulphonyl* derivative (II; R = NH·NH·SO_2Ph), prepared from (II; R = NH·NH_2) (3·1 g.) in exactly the same way as the isomer, crystallised from ethanol (charcoal) in buff-coloured needles, m. p. 188° (decomp.) (Found: C, 58·3; H, 4·6; N, 10·2%).

Degradation of 2-*Benzenesulphonhydrazido*-6-*methyl*cyclo*heptatrienone* (I; R = NH·NH·SO_2Ph).—To a solution of (I; R = NH·NH·SO_2Ph) (m. p. 124°) (1·0 g.) in ethylene glycol (25 c.c.), heated in an oil-bath to 140°, was added anhydrous sodium carbonate (2 g.). Heating was continued for 5 minutes after the vigorous evolution of gas had subsided, and the dark brown mixture was cooled, diluted with water, and extracted with chloroform. The chloroform solution was washed with water and extracted three times with 4N-hydrochloric acid (30 c.c.), and, after being washed with chloroform, the acid extract was neutralised with sodium hydrogen carbonate, and the oil isolated with ether. The product showed no ketonic properties, gave no colour with ferric chloride, and did not yield a picrate with an aqueous solution of picric acid.

The oil (0·2 g.) was shaken in ethanolic solution with hydrogen over a 10% palladium–charcoal catalyst until there was no further absorption; 97 c.c. (2·6 mols.) of hydrogen were absorbed. The filtered solution gave a sweet-smelling oil, which yielded 3-methyl*cyclo*heptanone semicarbazone, m. p. 179—180° after several crystallisations from ethyl acetate (Found: C, 58·6; H, 9·5; N, 23·1. Calc. for $C_9H_{17}ON_3$: C, 59·0; H, 9·4; N, 23·0%). This melting point was not depressed on admixture of the compound with an authentic specimen, m. p. 180—181°.

Degradation of 2-*Benzenesulphonhydrazido*-4-*methyl*cyclo*heptatrienone* (II; R = NH·NH·SO_2Ph).—(II; R = NH·NH·SO_2Ph) was hydrolysed under exactly similar conditions, and the acid-soluble fraction of the products was hydrogenated over a palladium catalyst, giving a neutral oil from which 4-methyl*cyclo*heptanone semicarbazone was prepared. After several crystallisations from ethyl acetate this had m. p. 158—160° (Found: C, 59·1; H, 9·7; N, 23·3%), undepressed on admixture of the specimen with an authentic specimen, m. p. 157—158°.

Action of Nitrous Acid on 2-*Hydrazino*-6-*methyl*cyclo*heptatrienone* (I; R = NH·NH_2).—To a solution of (I; R = NH·NH_2) (0·7 g.) in N/2-hydrochloric acid (12 c.c.), cooled in an ice-bath, was added a cold solution of sodium nitrite (0·32 g.). The resulting pale cream precipitate was collected and dissolved in absolute ethanol; the solvent was removed on a water-bath, giving a pale brown gum. To this was added 2N-sodium hydroxide (10 c.c.), and after being warmed for 2 minutes the mixture was cooled and extracted with ether. Evaporation of the extract yielded a dark brown viscous oil which was extracted several times with boiling *cyclo*hexane, from which, on concentration and cooling were obtained pale yellow leaflets, m. p. 112° (0·3 g.), of 2-*amino*-6-*methyl*cyclo*heptatrienone* (I; R = NH_2) (Found: C, 71·3; H, 6·9; N, 10·3%) which gave no depression in melting point when mixed with a specimen prepared as described on p. 3428.

Acidification of the alkaline mother-liquors from the ether extraction, and isolation with ether yielded a small quantity of a yellow solid, which crystallised from aqueous methanol in yellow needles, m. p. 145°. This contained nitrogen (Found: N, 23·4%), was soluble in dilute hydrochloric acid, insoluble in sodium hydrogen carbonate solution, and gave no ferric colour, but was not obtained in sufficient quantity for identification.

Our thanks are due to the Department of Scientific and Industrial Research for maintenance allowances to two of us and to Imperial Chemical Industries Limited for a grant towards the expenses of this investigation.

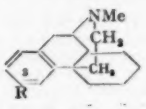
THE UNIVERSITY, SHEFFIELD, 10. [*Received, August 18th*, 1951.]

756. α-*Methylbenzylamines. Part II.** 3-cyclo*Hexyloxy*-4-*hydroxy*-α-*methylbenzylamine, Its Deoxy-derivative, and Related Ethers.*

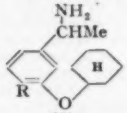
By A. McCoubrey and (in part) N. K. Iyengar.

3-*cyclo*Hexyloxy-4-hydroxy-α-methylbenzylamine, 4-*cyclo*hexyloxy-3-hydroxy-α-methylbenzylamine, and ethers of *m*- and *p*-hydroxy-α-methylbenzylamine have been prepared by conventional methods for biological evaluation.

While investigating the influence of chemical structure on biological activity in the morphine group of alkaloids, Small *et al.* ("Studies on Drug Addiction," U.S. Public Health Suppl., 1938, No. 138) found that alkylation ("muzzling") of the phenolic hydroxyl group in morphine and its derivatives practically always gave the same pharmacological results, irrespective of the nature of other changes in the morphine molecule. These effects were a reduction in most morphine-like activities including the analgesic potency, but usually an increase in toxicity and convulsant activity. Recently it has been found that the analgesic potency (of the order of morphine) of *N*-methylmorphinan (I; R = H) is markedly increased by introduction of hydroxyl at position 3 (Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 376; Zager, Sawtelle, Gross, Nagyfy, and Tidrick, *J. Lab. Clin. Med.*, 1949, **34**, 1530; Gross, Brotman, Nagyfy, Sawtelle, and Zager, *Fed. Proc.*, 1949, **8**, 297). The influence, on analgesic potency, of the position of the hydroxyl group is discussed by Grüssner and Schnider (*Helv. Chim. Acta*, 1949, **32**, 821). It appears that, so far as the morphine ring system is concerned, a suitably located phenolic hydroxyl potentiates the analgesic action. Though there is no reason to suppose that a similar effect would operate in other series of analgesics—thus, inclusion of a *m*-hydroxyl group in pethidine is reported to have no influence on analgesic potency (Macdonald, Woolfe, Bergel, Morrison, and Rinderknecht, *Brit. J. Pharmacol.*, 1946, **1**, 4)—it was desirable nevertheless to determine (*a*) whether demethylation of (II; R = OMe) would enhance the weak analgesic activity which had been detected in this substance (cf. McCoubrey, *J.*, 1951, 2931) and also reduce toxicity, and (*b*) whether the deoxy-derivative would have decreased or increased activity. The synthesis of suitable α-methylbenzylamines was therefore undertaken.



(I)



(II)

(III)

Treatment of 4-acetocatechol (III; R = R′ = H) with *cyclo*hexyl bromide and alkali gave only a poor yield of an easily separable mixture of 3-*cyclo*hexyloxy-4-hydroxy- and 4-*cyclo*hexyloxy-3-hydroxy-acetophenone: the reaction was largely inhibited by precipitation of the sodium salt of 4-acetocatechol. The desired product (III; R = H, R′ = *cyclo*hexyl) was only present in small proportion. The products were distinguished by methylation and comparison with the known 3-*cyclo*hexyloxy-4-methoxyacetophenone. The greater facility with which the *p*-hydroxyl group of 4-acetocatechol is etherified, which is in accordance with the expected electronic displacements, was also evident on monobenzylation since the major product proved to be 4-benzyloxy-3-hydroxyacetophenone (III; R = CH_2Ph, R′ = H), the structure of which was established by conversion into the *cyclo*hexyl ether followed by catalytic debenzylation to give 3-*cyclo*hexyloxy-4-hydroxyacetophenone, identical with that obtained directly from 4-acetocatechol. 3-*cyclo*Hexyloxy-4-hydroxy-α-methylbenzylamine and its 4-*cyclo*hexyloxy-3-hydroxy-isomer were readily obtained by reducing the corresponding acetophenone oximes. The corresponding deoxy-derivatives were similarly synthesised from the *cyclo*hexyl ethers of *m*- and *p*-acetylphenol.

A preliminary pharmacological examination indicated that whereas the phenol (II; R = OH) has approximately the same analgesic potency in rats as the methyl ether (II; R = OMe), the deoxy-derivative is more active. Also, *p*-*cyclo*hexyloxy-α-methylbenzylamine has a somewhat higher activity than its *m*-hydroxy-derivative. It was decided at this point, in view of the relative inaccessibility of *cyclo*hexyl ethers, to investigate the influence of the etherifying alkyl group on activity and to this end the *cyclo*pentyl, ethyl, *iso*propyl,

* Part I, *J.*, 1951, 2931.

n-amyl, *n*-hexyl, and *n*-octyl ethers were prepared from *p*-acetylphenol, and their oximes reduced to the corresponding α-methylbenzylamines. *p*-Phenoxy-α-methylbenzylamine (Ingersoll, Brown, Kim, Beauchamp, and Jennings, *J. Amer. Chem. Soc.*, 1936, **58**, 1808) was also synthesised for comparison. Noteworthy activity was confined to the higher ethers, but the phenyl analogue proved to be almost inactive.

Most of these amine hydrochlorides show anomalous solubilities similar to those already noted by Ingersoll *et al.* (*loc. cit.*) and examined in 2-amino-*n*-octane by Mann (*J.*, 1944, **456**; 1950, 3384).

Solubility in non-ionising solvents increases as the length of the alkyl chain is increased; lower members are easily soluble in benzene. The hydrochlorides of the amyl and hexyl ethers are not precipitated when hydrogen chloride is passed into a dry ethereal solution of the base although the solid hydrochlorides are not appreciably soluble in ether; the octyl ether hydrochloride, however, is easily soluble in ether and is readily soluble in warm light petroleum. The free bases, like α-methylbenzylamine and 2-phenylethylamine, readily absorb atmospheric carbon dioxide.

Experimental.

cyclo*Hexyl Ethers of* 4-*Acetocatechol*.—4-Acetocatechol (Stephen and Weizmann, *J.*, 1914, **105**, 1051) (60 g.) and *cyclo*hexyl bromide (160 g.) were refluxed in alcohol (200 c.c.) while sodium hydroxide (39·5 g.) in methanol (240 c.c.) was added during 50 hours. The sodium derivative of acetocatechol was deposited as a hard cake. The supernatant liquid was decanted and evaporated and the residue acidified. The precipitated oil was extracted with ether, and the extract washed with N-sodium hydroxide. The alkaline washings were acidified with 2N-hydrochloric acid, the phenols were shaken out with ether, and the extract was dried (K_2CO_3) and evaporated. The tarry residue (36·2 g.) was repeatedly extracted with boiling light petroleum (b. p. 80—100°) and the extracts were evaporated. The residual oil (12·8 g.) was dissolved in hot benzene (20 c.c.), and light petroleum (b. p. 80—100°) (15 c.c.) was added. On cooling, 4-cyclo*hexyloxy*-3-*hydroxyacetophenone* (A) (5·6 g.) was obtained which was recrystallised from benzene–light petroleum (b. p. 80—100°) in rosettes of needles, m. p. 103° (Found: C, 71·7; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The mother-liquors were evaporated and dissolved in 70% alcohol. On spontaneous evaporation two types of crystals were distinguished which were separated into (A), and long efflorescent prisms (3-cyclo*hexyloxy*-4-*hydroxyacetophenone*) (B). The latter crystallised from light petroleum (b. p. 80—100°) in long prisms, m. p. 88° (Found: C, 72·3; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The final yields were (A), 7·2 g., and (B), 1·5 g. It was subsequently found that separation of (A) and (B) could be effected by dissolution of the mixed phenols in warm N-sodium hydroxide and addition of an equal volume of 50% sodium hydroxide solution. On cooling, the solution set to a pasty mass which was filtered. The filtrate contained (A) and the residue was the sodium salt of (B).

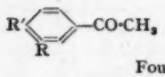
Methylation.—3-*cyclo*Hexyloxy-4-acetophenone (0·8 g.) in 10% sodium hydroxide solution (25 c.c.) at 50° was shaken with methyl sulphate (5 c.c.), added in 0·5-c.c. portions. The methyl ether (0·1 g.) crystallised from light petroleum (b. p. 60—80°) in white crystals, m. p. 60—61°, and gave a 2 : 4-dinitrophenylhydrazone, m. p. 191°. These were respectively identical by mixed m. p. with 3-*cyclo*hexyloxy-4-methoxyacetophenone and its 2 : 4-dinitrophenylhydrazone (McCoubrey, *loc. cit.*). Unchanged starting material (0·5 g.) was recovered.

4-*cyclo*Hexyloxy-3-hydroxyacetophenone (0·5 g.) similarly gave a methyl ether (0·5 g.), m. p. 86—87° [from benzene–light petroleum (b. p. 60—80°)]. Analysis of different samples did not give a satisfactory result (Found: C, 71·7, 71·6, 71·8; H, 7·9, 7·7, 8·2; OMe, 14·3. Calc. for $C_{15}H_{20}O_3$: C, 72·6; H, 8·1; OMe, 12·5%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red needles, m. p. 158° (Found: C, 58·9; H, 6·1; N, 13·3. $C_{21}H_{24}O_6N_4$ requires C, 58·9; H, 5·6; N, 13·1%).

Benzyl Ethers of 4-*Acetocatechol*.—Potassium hydroxide (7 g.) in aqueous methanol (50%; 50 c.c.) was added during 1 hour to a refluxing solution of 4-acetocatechol (19 g.) and benzyl chloride (15 c.c.) in alcohol (200 c.c.). Alcohols were evaporated and the residue was acidified. The precipitated oil was shaken out with ether, and the extract washed several times with N-sodium hydroxide and dried (K_2CO_3). Evaporation gave 3 : 4-*dibenzyloxyacetophenone* (1·9 g.) which crystallised from alcohol in needles, m. p. 89° (Found: C, 79·5; H, 6·4. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red plates, m. p. 184° (Found: N, 10·8. $C_{28}H_{24}O_6N_4$ requires N, 10·9%). The alkaline washings were acidified and the crystalline precipitate of 4-*benzyloxy*-3-*hydroxyacetophenone* recrystallised from alcohol in prisms (16 g.), m. p. 118° (Found: C, 74·6; H, 5·8. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%).

4-*Benzyloxy*-3-cyclo*hexyloxyacetophenone*.—4-Benzyloxy-3-hydroxyacetophenone (23·5 g.) was converted into its *cyclo*hexyl ether as described for 4-acetocatechol. Unchanged material (17·2 g.) was recovered. 4-*Benzyloxy*-3-cyclo*hexyloxyacetophenone*, b. p. 210—215° (bath-temp.)/0·6 mm., crystallised from light petroleum (b. p. 60—80°) in needles (7·8 g.), m. p. 76—77° (Found: C, 77·4; H, 7·4. $C_{21}H_{24}O_3$ requires C, 77·8; H, 7·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red needles, m. p. 182° (Found: N, 11·1. $C_{27}H_{28}O_6N_4$ requires N, 11·1%).

4-Benzyloxy-3-*cyclo*hexyloxyacetophenone (13·5 g.) in alcohol (100 c.c.) was shaken with hydrogen in the presence of palladised charcoal (30%; 1 g.) at atmospheric pressure and room temperature, 960 c.c. of hydrogen being absorbed during 8 hours. The solution was filtered and evaporated. The residue crystallised from light petroleum (b. p. 80—100°) in prisms (8·0 g.), m. p. 88°, identical (mixed m. p.) with the product (B) obtained from 4-acetocatechol.

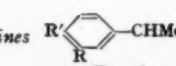
TABLE I. *Acetophenone derivatives* 

No.	R	R′	Yield, %	B. p./mm.	M. p.	Formula	Found, C, %	Found, H, %	Required, C, %	Required, H, %
1	H	O·C_6H_{11} [a]	23	145°/0·6	79°	$C_{14}H_{18}O_2$	76·9	7·9	77·1	8·3
2	OC_6H_{11} [a]	H	27	132—134°/0·8	—	$C_{14}H_{18}O_2$	—	—	—	—
3	H	O·C_5H_9 [c]	52	—	43	$C_{13}H_{16}O_2$	76·2	7·7	76·5	7·8
4	H	O·C_6H_{17}-*n*	64	215—222°/24	—	$C_{16}H_{24}O_2$	—	—	—	—
5	H	O·C_6H_{13}-*n*	48	190—195°/16 [d]	—	$C_{14}H_{20}O_2$	—	—	—	—
6	H	O·C_5H_{11}-*n*	69	181—183°/18	30	$C_{13}H_{18}O_2$	75·3	8·6	75·7	8·7
7	H	OPr^i	—	—	22	$C_{11}H_{14}O_2$	—	—	—	—
8	OPr^i	H	72	150°/13 [d]	—	$C_{11}H_{14}O_2$	—	—	—	—
9	OPr^i	OMe	80	165—166°/15	56	$C_{12}H_{16}O_3$	69·5	7·6	69·2	7·7
10	OPr^i	O·CH_2Ph	84	230—235°/8 [d]	62	$C_{18}H_{20}O_3$	76·1	7·3	76·1	7·0
11	OEt [b]	H	—	—	—	$C_{10}H_{12}O_2$	—	—	—	—

[a] C_6H_{11} = *cyclo*hexyl. [b] From ethylation of *p*-acetylphenol (Gatterman *et al.*, *Ber.*, 1890, **23**, 1199). [c] C_5H_9 = *cyclo*pentyl. [d] Bath-temp.

	Oxime						2 : 4-Dinitrophenylhydrazone		
	Found			Required				Found,	Reqd.,
No.	M. p.	C, %	H, %	N, %	C, %	H, %	N, %	M. p.	N, %	N, %
1	122°	71·6	8·0	6·1	72·1	8·2	6·0	—	—	—
2	84	72·1	8·1	5·8	72·1	8·2	6·0	167°	14·0 [e]	14·1
3	135	—	—	6·3	—	—	6·4	—	—	—
4	67	—	—	5·3	—	—	5·3	135	13·1	13·1
5	79	—	—	6·0	—	—	6·0	141	14·2	14·0
6	78	—	—	6·2	—	—	6·3	—	—	—
7	112	68·4	7·7	7·2	68·4	7·8	7·2	194	15·6	15·6
8	—	—	—	—	—	—	—	143	15·2 [f]	15·6
9	75	—	—	6·4	—	—	6·3	180	14·0	14·4
11	122	—	—	7·7	—	—	7·8	—	—	—

[e] Found: C, 60·7; H, 5·5. Reqd.: C, 60·3; H, 5·5%. [f] Found: C, 56·4; H, 4·8. Reqd.: C, 57·0; H, 5·0%.

TABLE II. *Substituted α-methylbenzylamines* 

R	R′	Yield, %	B. p./mm. [a]	M. p. of hydrochloride	Formula	Found, C, %	Found, H, %	Found, N, %	Required, C, %	Required, H, %	Required, N, %	Solvent [b]
H	O·C_6H_{11} [c]	73	175—180°/16	180°	$C_{14}H_{21}ON,HCl$	65·4	8·5	5·5	65·8	8·6	5·5	B–P
O·C_6H_{11} [c]	H	85	150°/0·5	—	$C_{14}H_{21}ON$	76·1	9·9	6·1	76·7	9·6	6·4	—
H	O·C_5H_9 [d]	50	—	181	$C_{13}H_{19}ON,HCl$	64·9	8·4	5·4	64·6	8·3	5·8	B–E
H	O·C_6H_{17}-*n*	56	—	68—70	$C_{16}H_{27}ON,HCl$	66·9	9·6	4·6	67·2	9·8	4·9	P
H	O·C_6H_{13}-*n*	53	170—175°/20	88—89	$C_{14}H_{23}ON,HCl$	65·0	9·2	5·2	65·2	9·3	5·4	B–P
H	O·C_5H_{11}-*n*	91	170—175°/16	76—78	$C_{13}H_{21}ON,HCl$	64·1	8·8	5·6	64·1	9·2	5·8	B–P
OPr^i	H	78 [e]	145°/13	86	$C_{11}H_{17}ON,HCl$	61·2	8·4	6·5	60·7	8·3	6·6	B–P
OH	O·C_6H_{11} [c]	95	—	111 [f]	$C_{14}H_{21}O_2N$	70·8	9·1	—	71·4	9·0	—	B
				270	$C_{14}H_{21}O_2N,HCl$	62·1	8·3	5·2	61·9	8·1	5·2	A–Ac
OPr^i	OMe	80	—	166	$C_{13}H_{19}O_2N,HCl$	58·4	8·1	—	58·7	8·2	—	A–E
OH	O·C_6H_{11} [c]	76 [g]	—	258 [g]	$C_{14}H_{21}O_2N,HCl$	61·1	8·0	5·9	61·9	8·1	5·2	B–A
H	OPr^i	84	150—170°20	122	$C_{11}H_{17}ON,HCl$	60·7	8·3	6·5	61·2	8·4	6·5	B–P
OH	OPr^i	39 [g]	—	198 [h]	$C_{11}H_{17}O_2N,HCl$	58·0	7·7	5·8	57·0	7·8	6·0	B–A
H	OEt	76	200—205°/33	204	$C_{10}H_{15}ON,HCl$	59·6	8·0	7·0	59·6	7·9	6·9	B–A

[a] C_6H_{11} = *cyclo*hexyl. [b] C_5H_9 = *cyclo*pentyl. [c] Bath-temp. [d] M. p. of base. [e] Dried at 100°/10 mm. to remove benzene of crystallisation. Undried crystals have m. p. 175°, resolidify, and remelt at 252—258° (Found: C, 64·2; H, 7·7; N, 4·7; loss at 100°/10 mm., 8·3. $C_{14}H_{21}O_2N,HCl,0{\cdot}33C_6H_6$ requires C, 64·5; H, 8·1; N, 4·7; loss, 8·7%). [f] Dried at 140°/10 mm. to remove benzene of crystallisation. Undried crystals have m. p. 198° (Found: C, 63·4; H, 7·7; N, 4·6; loss at 140°/10 mm., 13·4. $C_{11}H_{17}O_2N,HCl,0{\cdot}66C_6H_6$ requires C, 63·5; H, 7·7; N, 4·9; loss, 13·4%). [g] Calc. on ketone used. [h] A = alcohol; Ac = acetone; B = benzene; E = ether; P = light petroleum (b. p. 60—80°).

p-*Acetylphenol*.—This was prepared in 48% yield from phenol, acetic anhydride, and aluminium chloride (3 mols.) in carbon disulphide. von Auwers and Mauss (*Annalen*, 1928, **460**, 274) report a 70% yield for a similar method using acetyl chloride.

Various Etherifications.—Various *ethers* prepared are shown in Table I. *cyclo*Hexyl ethers were prepared by the method previously described. Other ethers were prepared by refluxing the phenol with two molecular proportions of alkyl bromide and addition of two molecular proportions of methanolic sodium hydroxide during 1 hour.

(±)-α-*Methylbenzylamines*.—The corresponding oximes were reduced in 90% methanol by addition of sodium amalgam (3%) and acetic acid in small portions. The amines, isolated in the usual manner, were converted into the hydrochlorides. The *amines* and *salts* prepared are listed in Table II.

The authors thank Professor F. Challenger, D.Sc., F.R.I.C., in whose laboratories most of this work was carried out during tenure of a Beit Memorial Fellowship for Medical Research.

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[*Received, July 30th*, 1951.]

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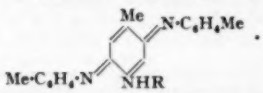
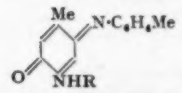
757. *Studies in Peroxidase Action. Part VII.* The Oxidation of* p-*Toluidine by Hydrogen Peroxide in the Presence of Ferrous Sulphate.*

By D. G. H. DANIELS, F. T. NAYLOR, and B. C. SAUNDERS.

The action of hydrogen peroxide in the presence of the enzyme peroxidase at pH 4·5 on *p*-toluidine has already been investigated. It is now shown that, if the reaction is catalysed by ferrous ions, instead of by peroxidase, a considerable amount of amorphous material is produced together with small quantities of 2 : 7-dimethyl-3-*p*-toluidinophenazine and 4 : 4′-dimethylazobenzene. Traces of di-*p*-tolylamine, 4-*p*-toluidino-2 : 5-toluquinone di-*p*-tolylimine, and 4-*p*-toluidino-2 : 5-toluquinone 2-*p*-tolylimine have also been isolated. The ferrous-catalysed oxidation is therefore not identical with that catalysed by the enzyme.

IN Part II (Saunders and P. J. G. Mann, *J.*, 1940, 769) it was shown that the oxidation of *p*-toluidine by hydrogen peroxide, catalysed by the enzyme peroxidase, produced mainly 4-amino-2 : 5-toluquinone di-*p*-tolylimine (I; R = H), 4-*p*-toluidino-2 : 5-toluquinone di-*p*-tolylimine (I; R = *p*-C_6H_4Me), and di-*p*-tolylamine. Traces of 4 : 4′-dimethylazobenzene, 4-amino-2 : 5-toluquinone 2-*p*-tolylimine (II; R = H), and 4-*p*-toluidino-2 : 5-toluquinone 2-*p*-tolylimine (II; R = *p*-C_6H_4Me) were also produced. These compounds accounted for nearly the whole of the solid oxidation product.

(I)  (II) 

In contrast to this result, we have now shown that if ferrous sulphate is substituted for peroxidase, the rapid reaction which ensues leads mainly to amorphous material. From the mixture we have isolated only traces of 4-*p*-toluidino-2 : 5-toluquinone di-*p*-tolylimine (I; R = *p*-C_6H_4Me), 4-*p*-toluidino-2 : 5-toluquinone 2-*p*-tolylimine (II; R = *p*-C_6H_4Me), di-*p*-tolylamine, and 4 : 4′-dimethylazobenzene. Moreover, there was produced in larger amount a compound which crystallised in orange prisms, m. p. 206—207°, not obtained in the peroxidase oxidation. It showed a strong yellow-green fluorescence in dilute benzene solution, and gave a characteristic green colour with concentrated sulphuric acid, changing to magenta on dilution.

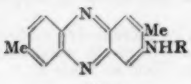
This compound, a base, had the empirical formula $C_{21}H_{19}N_3$. Two series of salts were formed: green, stable only in the presence of excess of concentrated acid, and reddish-violet. These were evidently di- and mono-acid salts respectively. The chloroplatinate, picrate, and picrolonate, all violet, were prepared. It was reversibly reduced to a leuco-compound.

These facts suggested that it might be 2 : 7-dimethyl-3-*p*-toluidinophenazine (III; R = *p*-C_6H_4Me) derived from the union of three *p*-toluidine residues. This supposition was confirmed by synthesis by two independent routes.

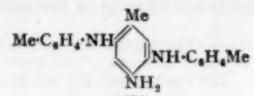
In the first, oxidation of 2 : 5-di-*p*-toluidino-*p*-toluidine (IV) by means of lead dioxide gave (III; R = C_6H_4Me) directly. The reaction giving (I; R = H) and not involving ring-closure predominated, however.

* Part VI, *J.*, 1951, 2112.

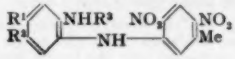
In the second, 3-amino-2 : 7-dimethylphenazine (III; R = H) was prepared by the stannous chloride reduction of 2-amino-4 : 5′-dimethyl-2′ : 4′-dinitrodiphenylamine (V; R^1 = Me, R^2 = R^3 = H) (cf. Ullmann, *Annalen*, 1909, **366**, 91). This compound resulted from the condensation of 3 : 4-diaminotoluene and 5-bromo-2 : 4-dinitrotoluene. Its structure was



(III)



(IV)



(V)

established by the formation of an acetyl derivative, which was identical with the compound (V; R^1 = Me, R^2 = H, R^3 = Ac) from the condensation of 3-acetamido-4-aminotoluene with 5-bromo-2 : 4-dinitrotoluene, and depressed the m. p. of the compound (V; R^1 = H, R^2 = Me, R^3 = Ac) from the condensation of 4-acetamido-3-aminotoluene with 5-bromo-2 : 4-dinitrotoluene. 3-Amino-2 : 7-dimethylphenazine decomposed very rapidly in air. It was characterised by its light absorption and by its acetyl derivative, m. p. 258—260°. 2 : 7-Dimethyl-3-*p*-toluidinophenazine, identical with the oxidation product, was formed by heating 3-amino-2 : 7-dimethylphenazine with *p*-toluidine and hydrochloric acid in a sealed tube filled with nitrogen.

Experimental.

Oxidation of p-*Toluidine.*—*p*-Toluidine (20 g.) was dissolved in acetic acid (23 g.) and diluted with water (1 l.). To this solution was added hydrogen peroxide (2 c.c.; 20-vol.), no colour being produced. Ferrous sulphate solution (*ca.* 1 c.c.; 5% of hydrate) was added, and a magenta colour was produced immediately. Hydrogen peroxide (200 c.c.) and ferrous sulphate solution (*ca.* 12 c.c.) were added over a period of 50 hours. A brown precipitate gradually separated and was filtered off at the conclusion of the reaction, and dried (yield, 8—10 g.). If hydrogen peroxide was added too quickly a strong odour of *iso*cyanide was noticed.

Treatment of the Crude Oxidation Product.—The dry crude product (25 g.) was extracted in a Soxhlet apparatus with *cyclo*hexane. The extract was evaporated and the solid residue (4·1 g.) was dissolved in chloroform. Chromatography on alumina gave a preliminary purification. The eluate was evaporated to dryness, dissolved in benzene, and re-chromatographed, the bands being collected as a "liquid chromatogram." They appeared in the following order :

(i) 4 : 4′-*Dimethylazobenzene.* On concentration of the eluate, deep yellow crystals were obtained which, when recrystallised from light petroleum (b. p. 60—80°), had m. p. 143—144° and gave a yellow colour with concentrated sulphuric acid in the cold. This is the behaviour of 4 : 4′-dimethylazobenzene, m. p. 145°.

(ii) 4-p-*Toluidino*-2 : 5-*toluquinone di*-p-*tolylimine.* The eluate gave, on evaporation, a small amount of an oil which crystallised on cooling. This consisted of a mixture of the toluquinone derivative and di-*p*-tolylamine. When recrystallised from benzene the ditolylamine remained in the mother-liquor and 4-*p*-toluidino-2 : 5-toluquinone di-*p*-tolylimine separated as red needles, m. p. 178—179°, on cooling. With concentrated sulphuric acid the toluquinone gave a characteristic violet colour, rapidly changing to green.

(iii) *Di*-p-*tolylamine.* Evaporation of the eluate from band (iii) gave a very small quantity of di-*p*-tolylamine contaminated with traces of 4 : 4′-dimethylazobenzene. Purification consisted of vacuum-sublimation, followed by reduction of 4 : 4′-dimethylazobenzene to *p*-toluidine by treatment with tin and dilute hydrochloric acid in which the ditolylamine is sparingly soluble. Extraction with light petroleum yielded the compound as needles, m. p. 78—79°.

(iv) 2 : 7-*Dimethyl*-3-p-*toluidinophenazine.* The eluate of this band was concentrated; orange prisms of 2 : 7-*dimethyl*-3-p-*toluidinophenazine* separated on cooling. A further quantity was obtained from the residue in the mother-liquor by sublimation at 170—180°/2 × 10^{-4} mm. After recrystallisation from benzene it had m. p. 206—207° (yield, 0·75 g.) (Found : C, 80·7; H, 6·2; N, 13·7. $C_{21}H_{19}N_3$ requires C, 80·5; H, 6·1; N, 13·4%). Dilute solutions in benzene showed a strong yellow-green fluorescence in ultra-violet light. Crystallisation from aqueous alcohol gave red needles, m. p. 206°, which did not depress the m. p. of the orange variety crystallised from benzene. The red variety also resulted from sublimation in a high vacuum, and was immediately changed to orange when moistened with benzene. Concentrated mineral acids gave green solutions which changed to reddish-violet on dilution. Light absorption in light petroleum : Max., 2450, 2820, 3720, and 4340 Å; ε = 37,000, 39,200, 8860, and 12,300, respectively. Light absorption in concentrated sulphuric acid : Max., 2440, 2990, 4120, 4820, and 6550 Å; ε = 59,400, 38,400, 7600, 14,500, and 11,400, respectively. Light absorption in 10% sulphuric acid : Max., 2380, 3020, 4200, and 5350 Å; ε = 46,200, 33,900, 14,500, and 20,900, respectively.

The following derivatives were readily prepared : *Chloroplatinate :* violet needles from methanol, no m. p. [Found : C, 48·3; H, 4·1; N, 7·7; Pt, 17·75. $(C_{21}H_{19}N_3)_2,H_2PtCl_6,2CH_3·OH$ requires C, 48·0; H, 4·4; N, 7·6; Pt, 17·75%]. *Picrate :* reddish-violet needles from ethanol, no m. p., decomp. *ca.* 225° (Found : C, 60·0; H, 4·3; N, 15·4. $C_{21}H_{19}N_3,C_6H_3O_7N_3$ requires C, 59·8; H, 4·1; N, 15·5%). *Picrolonate :* reddish-violet leaflets from ethanol, no m. p., decomp. *ca.* 215° (Found : C, 64·5; H, 4·8; N, 17·1. $C_{21}H_{19}N_3,C_{10}H_8O_5N_4$ requires C, 64·5; H, 4·7; N, 17·0%).

4-p-*Toluidino*-2 : 5-*toluquinone* 2-p-*Tolylimine*.—The original extract was shaken with aqueous hydrochloric acid (6N.), and a brownish-black precipitate was obtained (from this the phenazine could be isolated). The liquid was filtered, and the aqueous layer made alkaline and extracted with ether. A very small quantity of deep brown-red crystals, m. p. 177°, was obtained on concentrating the ether layer. These crystals gave a transient green colour with concentrated sulphuric acid, and on dilution gave a yellow solution. This is the behaviour of 4-*p*-toluidino-2 : 5-toluquinone 2-*p*-tolylimine (cf. Bornstein, *Ber.*, 1901, **34**, 1279, who gave m. p. 177°).

Oxidation of 2 : 5-*Di*-p-*toluidino*-p-*toluidine*.—This base was prepared from 4-amino-2 : 5-toluquinone di-*p*-tolylimine by reduction with zinc dust and glacial acetic acid (Green, *Ber.*, 1893, **26**, 2774). Excess of zinc was filtered off, and the filtrate diluted with hot water and allowed to cool slowly; almost colourless crystals, m. p. 164°, were obtained.

The compound (1·75 g.), mixed intimately with lead dioxide (7 g.), was heated slowly in a high vacuum. Sublimation commenced at 240°/2 × 10^{-4} mm. The orange-yellow sublimate was dissolved in light petroleum and chromatographed on alumina. Three bands were obtained which were eluted with ethanol: (i) This contained 4-amino-2 : 5-toluquinone di-*p*-tolylimine formed by re-oxidation of the leuco-base; its identity was confirmed by its characteristic blue coloration with concentrated sulphuric acid. (ii) On evaporation of the ethanol a small amount of a pink-red solid was left, which on recrystallisation from light petroleum (b. p. 60—80°) had m. p. 204°; mixed m. p. with 2 : 7-dimethyl-3-*p*-toluidinophenazine from hydrogen peroxide reaction, 204°. It gave the characteristic green colour with concentrated sulphuric acid, becoming pink on dilution. (iii) This band contained a trace of solid which gave a reddish-brown colour with concentrated sulphuric acid: it was not further investigated.

2-*Amino*-4 : 5′-*dimethyl*-2′ : 4′-*dinitrodiphenylamine*.—3 : 4-Diaminotoluene (4 g.), prepared by catalytic reduction of 3-nitro-*p*-toluidine, was dissolved in alcohol and heated for 1½ hours under reflux with 5-bromo-2 : 4-dinitrotoluene (5·2 g.) and anhydrous sodium acetate (2 g.). The *compound* crystallised from the hot solution in orange needles. It was filtered off, washed with water, and recrystallised from ethanol: m. p. 190—192° (decomp.) (5·3 g., 88%) (Found: C, 55·8; H, 4·7; N, 19·0. $C_{14}H_{14}O_4N_4$ requires C, 55·6; H, 4·6; N, 18·6%). The acetyl derivative (yellow needles) had m. p. 250—253°.

2-*Acetamido*-5 : 5′-*dimethyl*-2′ : 4′-*dinitrodiphenylamine*.—4-Acetamido-3-nitrotoluene was reduced catalytically to 4-acetamido-*m*-toluidine, m. p. 130°. It reacted as above with 5-bromo-2 : 4-dinitrotoluene. The *derivative* recrystallised from ethanol as yellow needles, m. p. 259—265° (decomp.) (Found: N, 16·4. $C_{16}H_{16}O_5N_4$ requires N, 16·3%); mixed m. p. with the acetyl derivative of 2-amino-4 : 5′-dimethyl-2′ : 4′-dinitrodiphenylamine (below), 227—232°.

2-*Acetamido*-4 : 5′-*dimethyl*-2′ : 4′-*dinitrodiphenylamine*.—This was prepared similarly, from 5-bromo-2 : 4-dinitrotoluene and 3-acetamido-*p*-aminotoluidine. The latter was obtained by catalytic reduction of 3-acetamido-4-nitrotoluene, formed as the minor product of the nitration of aceto-*m*-toluidide. 2-*Acetamido*-4 : 5′-*dimethyl*-2′ : 4′-*dinitrodiphenylamine* crystallised in yellow needles, m. p. 253—256° (decomp.); mixed m. p. with the acetyl derivative of 2-amino-4 : 5′-dimethyl-2′ : 4′-dinitrodiphenylamine, 253—255° (decomp.) (Found: N, 16·4. $C_{16}H_{16}O_5N_4$ requires N, 16·3%).

Reduction of 2-*Amino*-4 : 5′-*dimethyl*-2′ : 4′-*dinitrodiphenylamine*.—The compound (2 g.), stannous chloride (*ca.* 10 g.), and concentrated hydrochloric acid (8 c.c.) were heated for 5 hours in a sealed tube at 120°. During the reaction, the mixture became dark red. After some while at room temperature, it was diluted three-fold and made alkaline with sodium hydroxide, and the red precipitate filtered off, washed, and dried. It was extracted with ether in an atmosphere of nitrogen. The red extract was chromatographed on alumina. A prominent orange band was eluted as an orange-coloured solution exhibiting a strong green fluorescence. On evaporation of the solvent, a semi-crystalline mass, probably containing 3-amino-2 : 7-dimethylphenazine, was left (yield, crude, 0·2 g., 14%). It recrystallised from benzene–light petroleum (b. p. 60—80°) as orange needles, m. p. 248—249° (decomp.), which rapidly darkened in air. Light absorption of 3-*amino*-2 : 7-*dimethylphenazine* in light petroleum: Max., 2220, 2630, 3690, and 4120 Å; ε = 32,300, 71,300, 9170, and 8070, respectively. 2-Aminophenazine has light absorption in ether: Max., 2650, 3650, and 4880 Å (Kehrmann, Havas, and Grandmougin, *Ber.*, 1914, **47**, 1886). With concentrated sulphuric acid, 3-amino-2 : 7-dimethylphenazine gave a brown colour, which became successively green and magenta on dilution. The *acetyl* derivative recrystallised from methanol as pale yellow needles, m. p. 258—260° (Found: C, 71·6; H, 5·7; N, 16·2. $C_{16}H_{15}ON_3$ requires C, 72·4; H, 5·7; N, 15·9%).

Reaction with p-*toluidine*. The aminophenazine (100 mg.) was mixed with *p*-toluidine hydrochloride (64 mg., 1 mol.) and *p*-toluidine (240 mg., 5 mols.), and heated in a sealed tube filled with nitrogen for 2 hours at 150—160°. After cooling, the residue was washed with methanol and basified, and the brown precipitate filtered, dried, and extracted with ether. After removal of the solvent the excess of *p*-toluidine in the residue was removed by sublimation (100°/15 mm.), and the residue dissolved in benzene and chromatographed. Orange crystals were obtained in small yield, and on recrystallisation from benzene–light petroleum had m. p. 204—205°; mixed m. p. with 2 : 7-dimethyl-3-toluidinophenazine from the hydrogen peroxide reaction, 204—205° (Found: N, 13·7. Calc. for $C_{21}H_{19}N_3$: N, 13·4%).

We are grateful to the Department of Scientific and Industrial Research for maintenance grants to two of us (D. G. H. D. and F. T. N.). Our thanks are offered to Mr. C. L. de Silva for help with some of the experimental work.

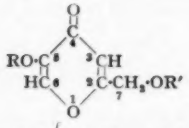
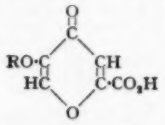
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 15th*, 1951.]

758. *The Mechanism of Alkaline Cleavage of Some γ-Pyrones.*

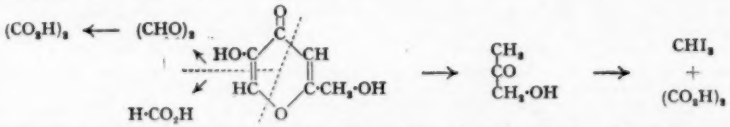
By H. R. V. Arnstein and Ronald Bentley.

The alkaline cleavage of the γ-pyrones, dimethylkojic acid and methylcomenic acid, has been investigated by the isotopic tracer technique. Dimethylkojic acid, labelled with ^{14}C in the methoxymethyl group, was cleaved either between carbon atoms 2 and 3 or between carbon atoms 3 and 4, although statistically the $C_{(2)}$–$C_{(3)}$ bond was broken more frequently. The hydrolysis products, methoxyacetone and methoxyacetic acid, can therefore arise from different carbon atoms. The hydrolysis of methylcomenic acid on the other hand did not give rise to any pyruvic acid and the cleavage in this case took place only between carbon atoms 2 and 3.

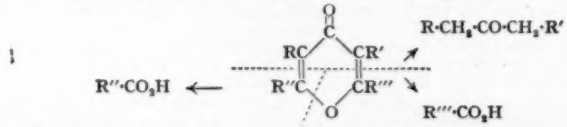
During an investigation of the biosynthesis of kojic acid (I; R = R′ = H) from ^{14}C-labelled precursors by various *Aspergilli* (Arnstein and Bentley, *Nature*, 1950, **166**, 948) an unequivocal method of degradation was required in order to locate the distribution of radioactive carbon in the molecule. According to Yabuta (*J. Chem. Soc. Japan*, 1916, **37**, 1185, 1234; *Chem. Abstr.*, 1923, **17**, 1475), the dimethyl derivative of (I) (R = R′ = Me) is cleaved by barium

(I)   (II)

hydroxide to give formic acid, methoxyacetic acid, and methoxyacetone. Similarly, kojic acid (I; R = R′ = H) is cleaved by alkaline hypoiodite to give formic acid, oxalic acid, iodoform, and glycollic acid as final products (Birkinshaw and Raistrick *Phil. Trans.*, *B*, 1931, **220**, 139). The mechanism of this breakdown of kojic acid was represented by Birkinshaw and Raistrick (*loc. cit.*) as follows:

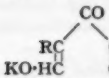


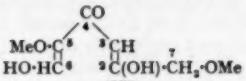
However, a comparison of the alkaline hypoiodite degradation of kojic acid with the alkaline hydrolysis of other γ-pyrones such as (II; R = Me), which is hydrolysed to oxalic acid, methoxyacetone, and formic acid, led us to believe that the alkaline hydrolysis of such γ-pyrones takes place by the following mechanism which differs from that postulated by Birkinshaw and Raistrick (*loc. cit.*) for the hypoiodite degradation:

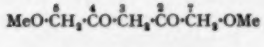


This conclusion appeared to be supported by the isolation of methoxyacetone from the hydrolysis products of 5-*O*-methylkojic acid (I; R = Me, R′ = H). On the basis of these observations we concluded that dimethylkojic acid yields formic acid arising from $C_{(6)}$, methoxyacetic acid from $C_{(2)}$ and $C_{(7)}$, and methoxyacetone from the remaining three carbon atoms of the molecule. However, in many experiments using different ^{14}C-labelled precursors it was observed that the radioactivity of the methoxyacetic acid arising from $C_{(2)}$ and $C_{(7)}$ of kojic acid was always almost exactly equal to the radioactivity of the methoxyacetic acid obtained by further degradation of the methoxyacetone with sodium hypoiodite. We therefore considered the possibility that the mechanism of hydrolysis of kojic acid resulted in randomisation of the label originally located in $C_{(4)}$, $C_{(5)}$, $C_{(2)}$, and $C_{(7)}$. Many γ-pyrones are split by alkali under mild conditions to give bishydroxymethylene compounds, usually as the potassium derivatives (III),

which are reconverted into γ-pyrones by acid. Dimethylkojic acid would similarly give (IV), which would be converted into the symmetrical diketone (V) by loss of the hydroxymethylene group (carbon atom 6). Further hydrolysis of (V) would yield methoxyacetic acid, arising


(III)


(IV)


(V)

from $C_{(4)}$ and $C_{(5)}$, or $C_{(2)}$ and $C_{(7)}$, and methoxyacetone arising from $C_{(3)}$, $C_{(2)}$, and $C_{(7)}$, or $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$.

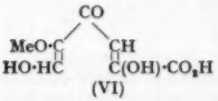
If such a mechanism existed, dimethylkojic acid labelled with ^{14}C in one of the two methoxyl groups should give rise to both methoxyacetic acid and methoxyacetone containing ^{14}C in the methoxyl group. Kojic acid 5 : 7[$^{14}C_1$]-dimethyl ether * (I; R = CH_3, R′ = $^{14}CH_3$) was therefore prepared by methylating 5-*O*-methylkojic acid (I; R = Me, R′ = H) with a slight excess of [^{14}C]methyl iodide. The possibility of exchange of the methoxyl group of 5-*O*-methylkojic acid with the [^{14}C]methyl iodide was excluded by showing that the specific radioactivity of the recovered [^{14}C]methyl iodide was identical with that of the starting material. Degradation of (I; R = CH_3, R′ = $^{14}CH_3$) with barium hydroxide, essentially as described by Yabuta (*loc. cit.*), afforded methoxyacetic acid, methoxyacetone, and formic acid. The formic acid was completely non-radioactive and the methoxyacetic acid and methoxyacetone together accounted for the whole of the radioactivity in the kojic acid dimethyl ether. However, the radioactivity in the methoxyacetic acid was about 1·2 times that in the methoxyacetone, as shown below, indicating a more frequent rupture of the $C_{(2)}$–$C_{(3)}$ bond than of the $C_{(3)}$–$C_{(4)}$ bond. Since cleavage of (V) would result in equal radioactivity in the methoxyacetic acid and the methoxyacetone, it is clear that (IV) is at least partly cleaved at the $C_{(2)}$–$C_{(3)}$ bond while the hydroxymethylene group is still intact.

Distribution of ^{14}C *in degradation products of kojic acid* 5 : 7[$^{14}C_1$]*-dimethyl ether.*

	Radioactivity *	
	counts/min.	counts/min./micromol.
Kojic acid 5 : 7[$^{14}C_1$]-dimethyl ether	500·6	85·2
Methoxyacetone 2 : 4-dinitrophenylhydrazone	138·8	37·2
" " " " recryst.	142·3	38·2
Silver methoxyacetate, *ex* kojic acid dimethyl ether	239·2	47·1
Silver methoxyacetate, *ex* methoxyacetone	194·8	38·4

* See Experimental section.

In view of the small but definite effect of the hydroxymethylene group on the cleavage of (IV) it was of interest to investigate the cleavage of *O*-methylcomenic acid (II; R = Me).


(VI)

A preliminary experiment showed that hydrolysis of this with barium hydroxide yielded an almost equimolecular quantity of barium oxalate. Nevertheless, it seemed possible that, by analogy with the cleavage of (IV), hydrolysis of a hypothetical intermediate (VI) might yield also some pyruvic acid. In the preliminary experiment, no pyruvic acid 2 : 4-dinitrophenylhydrazone could be isolated, but the possibility existed that under the conditions of the experiment the pyruvic acid might be destroyed.

The hydrolysis of *O*-methylcomenic acid was therefore repeated in the presence of a small excess of ethyl pyruvate. Although both methoxyacetone and pyruvic acid were easily isolated as the 2 : 4-dinitrophenylhydrazones, the latter was obtained only in poor yield, especially when the reaction mixture had been steam-distilled, indicating that under the conditions of the hydrolysis substantial destruction of pyruvic acid had occurred. As the amount of pyruvic acid expected from the hydrolysis of *O*-methylcomenic acid would be very small it seemed possible that owing to destruction during the reaction this hydrolysis product might not be detected by the above method. It was decided therefore to use the isotope dilution technique in order to detect the possible formation of pyruvic acid in this reaction. Since this method is based on dilution of radioactivity of pyruvic acid present during the entire course of the

* The symbol 5 : 7[$^{14}C_1$] indicates the position of labelling for R = CH_3, R′ = $^{14}CH_3$. The compound in which R = $^{14}CH_3$ and R′ = CH_3 would have the symbol 5[$^{14}C_1$] : 7. The compound in which both R and R′ are $^{14}CH_3$ would have the symbol 5 : 7[$^{14}C_2$]. Ed.

hydrolysis by any pyruvic acid which may be formed, it is independent of the subsequent destruction of part of this compound. When labelled sodium pyruvate, $CH_3 \cdot CO \cdot {}^{14}CO_2Na$, was added to the reaction mixture the specific radioactivity of the pyruvic acid 2 : 4-dinitrophenylhydrazone isolated at the end of the reaction was identical with that of the original pyruvic acid. No pyruvic acid had therefore been formed during the hydrolysis and the cleavage of *O*-methylcomenic acid must have occurred exclusively at the $C_{(2)}$–$C_{(3)}$ bond.

It seems likely, therefore, that substitution of γ-pyrones by an electron-attracting group at position 2, such as the carboxyl group in *O*-methylcomenic acid, greatly enhances the tendency to split preferentially at the $C_{(2)}$–$C_{(3)}$ bond.

Experimental.

Radioactivity Determinations.—All measurements were carried out on " infinite thickness " samples, *i.e.*, 25 mg. or more of material/sq. cm., mounted on 1 sq. cm. polythene discs, as described by Popják (*Biochem. J.*, 1950, **46**, 560). Samples were counted with a helium-filled bell-shaped Geiger–Müller counter which had a thin mica window. The " background " of the instrument was 8—10 counts/minute and a sample containing 10^{-3} μc of ^{14}C/mg. gave a counting rate of approx. 1100 counts/minute under the above conditions.

[^{14}C]*Methyl Iodide.*—[^{14}C]Methanol (obtained from the Radiochemical Centre, Amersham) was diluted with carrier methanol and converted into methyl iodide according to Tolbert (*J. Amer. Chem. Soc.*, 1947, **69**, 1529). A portion of this material was converted into the methylthiuronium picrate, which had 287·7 counts/minute. After recrystallisation from acetone the picrate had m. p. 224—225° and gave 262·1 counts/minute.

Kojic Acid 5 : 7[$^{14}C_1$]-Dimethyl Ether.—5-*O*-Methylkojic acid (1 g.), prepared from kojic acid as described by Campbell, Ackerman, and Campbell (*J. Org. Chem.*, 1950, **15**, 221), in boiling methanol (25 c.c.) was treated with silver oxide (4 g.) and [^{14}C]methyl iodide (5 c.c.) in two portions (Armit and Nolan, *J.*, 1931, 3023). The solution was filtered and evaporated to dryness. After being washed with ether the crude product (0·87 g.; 407 counts/minute) was recrystallised from chloroform by addition of ether and light petroleum (b. p. 60—80°), to give kojic acid dimethyl ether, m. p. 84—85° (417 counts/minute). Sublimation *in vacuo* afforded pure material, m. p. 88—89° (500·6 counts/minute).

Hydrolysis. To the above material (0·25 g.) in water (25 c.c.) was added barium hydroxide octahydrate (0·47 g.). After 30 minutes' heating at 100° the solution was kept at room temperature for 16 hours and then steam-distilled, 170 c.c. of distillate being collected. 60 C.c. of the distillate were treated with 2 : 4-dinitrophenylhydrazine in 6N-hydrochloric acid; methoxyacetone 2 : 4-dinitrophenylhydrazone (138·8 counts/minute) was filtered off and, recrystallised from ethanol, had m. p. 155° (142·3 counts/minute). The remainder of the steam-distillate was treated with excess of sodium hypoiodite. The iodoform, which was completely non-radioactive, was filtered off. The filtrate was acidified, iodine was removed by extraction with a small volume of ether, and the solution was continuously extracted with ether for 18 hours. The ethereal extract was evaporated to dryness and the residual methoxyacetic acid was dissolved in water (10 c.c.) and treated with finely ground silver carbonate. After filtration, the aqueous solution was concentrated *in vacuo* below 50° almost to dryness; on addition of ethanol, silver methoxyacetate was obtained as a flocculent precipitate (194·8 counts/minute).

The residue from the steam-distillation was acidified with sulphuric acid (1·5 c.c.) in water (10 c.c.). The barium sulphate was removed by centrifugation; the solution was refluxed with mercuric oxide (3 g.) in order to oxidise the formic acid to carbon dioxide, which was collected as barium carbonate and counted. The carbonate was completely non-radioactive. Excess of mercuric oxide was removed by filtration and methoxyacetic acid was isolated from the filtrate by continuous ether-extraction. The silver salt prepared as described above had 239·2 counts/minute.

Hydrolysis of O-Methylcomenic Acid.—Barium hydroxide octahydrate (2·33 g.) was added to a suspension of methylcomenic acid (0·85 g.) in hot water (50 c.c.). After 20 minutes at 100° the solution was filtered to remove barium oxalate (0·94 g., 84%). The filtrate was divided into two equal portions. One portion was acidified with concentrated hydrochloric acid and treated with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The 2 : 4-dinitrophenylhydrazone (0·35 g.) had m. p. 156—157° after chromatography on alumina; the mixed m. p. with authentic methoxyacetone 2 : 4-dinitrophenylhydrazone was not depressed. The second portion, which was neutral, was steam-distilled. One half of the distillate was converted into the 2 : 4-dinitrophenylhydrazone (0·118 g., 70·5%), m. p. and mixed m. p. with methoxyacetone 2 : 4-dinitrophenylhydrazone, 154—155° after recrystallisation from ethanol. The residue from the steam-distillation gave no precipitate with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. When the hydrolysis was repeated with methylcomenic acid (0·283 g.) and ethyl pyruvate (0·232 g.), the residue from the steam-distillation of one half of the reaction mixture gave a 2 : 4-dinitrophenylhydrazone (84 mg., 32%), m. p. 217—218° alone or mixed with authentic pyruvic acid 2 : 4-dinitrophenylhydrazone. The remainder of the reaction mixture was acidified with concentrated hydrochloric acid and treated with excess of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The precipitate was centrifuged and washed with water. An aqueous solution of sodium hydrogen carbonate was added and the insoluble portion of the precipitate was filtered off. The filtrate was acidified with 2N-hydrochloric acid, to give pyruvic acid 2 : 4-dinitrophenylhydrazone (125 mg., 47%), m. p. 213—214° alone or mixed with authentic material.

Hydrolysis of O-Methylcomenic Acid in Presence of $CH_3 \cdot CO \cdot {}^{14}CO_2H$.—Pyruvamide (2·4 mg.), labelled with ^{14}C in the carbamyl group, was hydrolysed by heating at 100° for 3 hours with 0·03 c.c. of N-hydrochloric acid in water (0·2 c.c.). Carrier sodium pyruvate (0·5 g.) was then added and the volume made

up to 30 c.c. A portion (10 c.c.) of this solution was converted into the 2 : 4-dinitrophenylhydrazone, m. p. 217—218°, which gave 974 counts/minute. The remainder of the above solution was added to methylcomenic acid (0·85 g.) suspended in water (20 c.c.). The hydrolysis was carried out with barium hydroxide octahydrate (2·23 g.) as described above. At the end of the hydrolysis pyruvic acid 2 : 4-dinitrophenylhydrazone was isolated from the reaction mixture. It had m. p. 217—218° and gave 973 counts/minute.

We thank Dr. G. Hunter for the ^{14}C-labelled pyruvamide and Dr. D. Herbert for a sample of pure sodium pyruvate. We are indebted to Dr. J. A. Barltrop for a helpful discussion concerning the mechanism of hydrolysis of kojic acid dimethyl ether.

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[*Received, August 24th,* 1951.]

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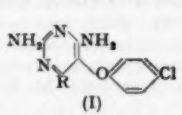
759. *Antimalarial Activity in 2 : 4-Diamino-5-arylpyrimidines. Some Reactions of α-Formylphenylacetonitrile.*

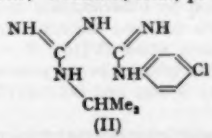
By B. H. CHASE, (MISS) J. P. THURSTON, and JAMES WALKER.

The effects of various agents on *Plasmodium gallinaceum* are briefly outlined in so far as " Paludrine " and certain pyrimidine types are concerned.

Reaction between α-formylphenylacetonitrile and diazomethane yielded a mixture of products containing the solid epoxide, βγ-epoxy-α-phenylbutyronitrile, as well as a solid enol methyl ether. Other methods for the preparation of enol ethers in good yield are described, and condensation of these ethers with guanidine affords, irrespective of their stereochemistry, good yields of 2 : 4-diamino-5-phenylpyrimidine. Direct condensation of α-formylphenylacetonitrile with guanidine gives the isomeric guanidinomethylenephenylacetonitrile, which, unexpectedly, passes into phenylacetylguanidine on treatment with acids. Similar reactions have been applied to *p*-chlorophenyl-α-formylacetonitrile. 2 : 4-Diamino-5-*p*-chlorophenylpyrimidine is highly active against *P. berghei* and *P. gallinaceum*, being about twice as active as " Paludrine " against both parasites in their respective hosts.

ALTHOUGH Curd and Rose and their colleagues proceeded in theory from sulphadiazine to pyrimidines and thence to diguanides in their development of " Paludrine " (proguanil) (*J.*, 1946, **343**, 729), the connection between pyrimidines and proguanil was purely speculative until Bishop and McConnachie (*Nature*, 1948, **162**, 541) linked sulphadiazine experimentally with proguanil by showing that certain proguanil-resistant strains of *P. gallinaceum* were cross-resistant to sulphadiazine and *vice versa*. Since that time it has been found that the antimalarial activity of proguanil was potentiated by *p*-aminobenzoic acid competitors, such as sulphadiazine (Greenberg, *J. Pharmacol.*, 1949, **97**, 238), that 2 : 4-diamino-6 : 7-diphenylpteridine could suppress parasitæmia in doses tolerated by chicks infected with *P. gallinaceum*, and that this action was potentiated by sulphadiazine and significantly inhibited by pteroylglutamic acid (*idem*, *ibid.*, p. 484), while the antimalarial action of sulphadiazine was potentiated by 2 : 4-diamino-5-aryloxypyrimidines (Greenberg and Richeson, *ibid.*, 1950, **99**, 444), which had previously been found to be powerful antagonists of pteroylglutamic acid in cultures of *L. casei* (cf. Hitchings, Elion, Falco, Russell, and VanderWerff, *Ann. N.Y. Acad. Sci.*, 1950, **52**, Art. 8, 1330). Falco, Hitchings, Russell, and VanderWerff (*Nature*, 1949, **164**, 107) noted that 2 : 4-diamino-5-*p*-chlorophenoxypyrimidine (I; R = H) showed a certain formal resemblance to proguanil (II), which they found also to be an effective antagonist of pteroylglutamic acid; conversely, the former (I; R = H) and a homologue (I; R = Me) were found to have antimalarial activity (Falco *et al.*, *loc. cit.*; Goodwin, *ibid.*, p. 1133).


(I)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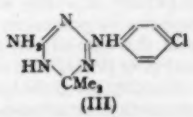
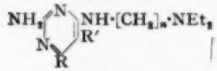
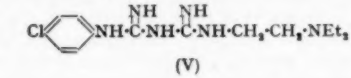

(III)

It may be recalled that it had been shown in these laboratories (Hawking, *Nature*, 1947, **159**, 409; Hawking and Perry, *Brit. J. Pharmacol.*, 1948, **3**, 320; Tonkin, *ibid.*, 1946, **1**, 163) that proguanil (II) *per se* does not appear to possess marked antimalarial activity but that it

undergoes activation in the animal body to give a substance of high intrinsic activity. The possibility that this activation product might be a cyclic structure is fairly obvious, having regard to the nature of the polyfunctionality of the diguanide chain in (II), although we have confirmed the fact that 6-amino-4-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-*s*-triazine (III), isolated by Crounse (Abst. of Papers, 117th Meeting, Amer. Chem. Soc., 1950, p. 28 L; *J. Org. Chem.*, 1951, **16**, 492) as a metabolite of proguanil, is devoid of activity (cf. Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645). Nevertheless, the possibility of a formal resemblance between the unknown active metabolite and 2 : 4-diaminopyrimidines did not appear to be excluded, and, together with the chain of circumstantial evidence outlined above, seemed to indicate the desirability for a further study of 2 : 4-diaminopyrimidines as antimalarials. Quite marked antimalarial activity had previously been observed in 4-dialkylaminoalkylamino-2-aminopyrimidines (IV) (Hull, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 357), and it was hoped that simplification of this type of compound by elimination of the dialkylaminoalkyl group to give simple 2 : 4-diaminopyrimidines would have a beneficial effect on activity similar to that produced by omitting the corresponding basic centre in passing from the inactive 1-*p*-chlorophenyl-5-2′-diethylaminoethyldiguanide (V) to the active compounds of the proguanil type (II) (Curd, Davey, and Rose, *Ann. Trop. Med. Parasitol.*, 1945, **39**, 208). The type selected for study was (VI; R = H or Cl), and we were unaware of the interest of others in this direction, but the appearance of a communication * by Falco, Goodwin, Hitchings, Rollo, and Russell (*Brit. J. Pharmacol.*, 1951, **6**, 185), following a brief preliminary report (*Chem. Eng. News*, 1951, **29**, 1508), obliges us to submit an account of a less extensive investigation along similar lines upon which we have recently been engaged.



(IV)



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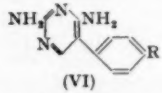
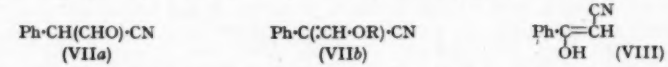


(VI)

The structure of α-formylphenylacetonitrile (VII*a*) has not been studied with the same thoroughness as has that of the less conveniently prepared ethyl α-formylphenylacetate, which exists almost entirely as the enol (cf. Eistert, Arndt, Loewe, and Ayça, *Chem. Ber.*, 1951, **84**, 159). The linearity of the cyano-group in (VII), however, prevents any contribution, through chelation, to the stability of the *cis*-form of the tautomeric hydroxymethylenephenylacetonitrile (VII*b*; R = H) (cf. Hendricks, Wulf, Hilbert, and Liddel, *J. Amer. Chem. Soc.*, 1936, **58**, 1991), although it gives a strong ferric reaction, whereas the isomeric ω-cyanoacetophenone gives no ferric reaction and is believed to form only a *trans*-enol (VIII) (Arndt and Loewe, *Ber.*, 1938, **71**, 1627). On the one hand, the reaction between ω-cyano-



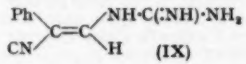
(VII*a*) (VII*b*) (VIII)

acetophenone and diazomethane proceeds quantitatively and homogeneously, both chemically and stereochemically, to give a solid enol ether (Arndt and Loewe, *ibid.*, p. 1631), while (VII), on the other hand, afforded with diazomethane two isomeric crystalline products together with oily material. One of these products, m. p. 176—178°, was methoxyl-free and, as it did not appear to react with the 2 : 4-dinitrophenylhydrazine reagent, was probably βγ-epoxy-α-phenylbutyronitrile, $Ph{\cdot}CH(CN){\cdot}CH\!-\!\underset{O}{\overset{}{}}\!-\!CH_2$; rearrangement to β-keto-α-phenylbutyronitrile, $Ph{\cdot}CH(CN){\cdot}CO{\cdot}CH_3$, is implicit in its facile hydrolysis to phenylacetic acid with alkali. The other crystalline product, m. p. 67—68°, was a pure stereoisomeric form of the enol methyl ether (VII*b*; R = Me). Better conversion into a mixture of the two stereoisomeric enol methyl ethers (VII*b*; R = Me) was obtained by etherification in dry acetone with methyl iodide in the presence of potassium carbonate (cf. von Auwers, *Ber.*, 1938, **71**, 2082), and excellent yields in the case of the enol *iso*butyl ether (VII*b*; R = Bu^i) were obtained by azeotropic distillation of (VII*a*) with *iso*butanol in benzene in the presence of a trace of toluene-*p*-sulphonic acid, following the technique used by Seifert and Schinz (*Helv. Chim. Acta*, 1951, **34**, 728) for hydroxymethylene ketones.

Reaction between the alkoxymethylenephenylacetonitriles (VII*b*; R = Me or Bu^i) and

* [*Added in proof, October 24th*, 1951.] Since this communication was submitted, three further relevant papers by Hitchings and his collaborators have come to hand (*J. Amer. Chem. Soc.*, 1951, **73**, 3753, 3758, 3763).

guanidine proceeded smoothly, and without being dependent, as far as yields were concerned, on the stereochemistry of the enol ether, to give 2 : 4-diamino-5-phenylpyrimidine (VI; R = H), as shown by comparison with an authentic specimen. The direct reaction, however, between formylphenylacetonitrile [(VII*a*) or (VII*b*; R = H)] and guanidine afforded in rather poor yield a product isomeric with (VI; R = H), which, as it was oxygen-free, must have been the *trans*-form (IX) of α-(guanidinomethylene)phenylacetonitrile, and, surprisingly, this substance passed readily into phenylacetylguanidine (X; Z = O) on acid hydrolysis. As a tentative mechanism for this transformation, which we hope to examine more closely, it may be that (IX) undergoes hydrolysis into its components with subsequent reaction of the guanidine with the cyano-group (cf. Russell and Hitchings, *J. Amer. Chem. Soc.*, 1950, **72**, 4922), fission of the formyl group, and hydrolysis of the resulting phenylacetimidoguanidine (X; Z = NH) to (X; Z = O).



(IX)

$Ph{\cdot}CH_2{\cdot}CZ{\cdot}NH{\cdot}C(:NH){\cdot}NH_2$
(X)

To establish the identity of (VI; R = H), an authentic specimen was prepared by dehalogenation of 2 : 4-diamino-6-chloro-5-phenylpyrimidine. In the preparation of 2 : 4 : 6-trichloro-5-phenylpyrimidine from 5-phenylbarbituric acid, following the technique of Baddiley and Topham (*J.*, 1944, 678), the extent to which the side reaction between the product and dimethylaniline interfered seemed to be greater than has hitherto been described (King, King, and Spensley, *J.*, 1947, 1247; Marshall and Walker, *J.*, 1951, 1004); the by-product was presumably 4 : 6-dichloro-2-methylanilino-5-phenylpyrimidine (cf. King, King, and Spensley, *loc. cit.*) rather than the 4-methylanilino-isomer. Reaction between the trichloropyrimidine and ammonia under suitable conditions stopped, as expected (cf. Basford, Curd, and Rose, *J.*, 1946, 714), with the introduction of two amino-groups, and dehalogenation of the resulting 2 : 4-diamino-6-chloro-5-phenylpyrimidine to (VI; R = H) took place smoothly on catalytic hydrogenation, in contrast with the difficulty experienced in effecting similar dehalogenation of 4-chloro- and 2 : 4-dichloro-5-phenylpyrimidine (Davies and Piggott, *J.*, 1945, 347). Application of reactions analogous to those described above to *p*-chlorophenyl-α-formylacetonitrile afforded successively α-*iso*butoxymethylene-*p*-chlorophenylacetonitrile and 2 : 4-diamino-5-*p*-chlorophenylpyrimidine (VI; R = Cl), and direct interaction with guanidine gave *p*-chlorophenyl-α-guanidinomethyleneacetonitrile, analogous with (IX).

Against *P. berghei* in the mouse, (VI; R = Cl) was active at a minimum effective dose of 0·1 mg./20 g. mouse (given intraperitoneally once daily for 4 days), whereas the minimum effective dose of proguanil under the same conditions was 0·2 mg./20 g.; (VI; R = Cl) was likewise about twice as effective as proguanil in *P. gallinaceum* infections in chicks, the minimum effective doses respectively being 0·5 mg./100 g. and 1 mg./100 g. *per os* b.i.d. × 3½. These results are comparable with those of Falco, Goodwin, Hitchings, Rollo, and Russell (*Brit. J. Pharmacol.*, 1951, **6**, 185), except that their strains of *P. berghei* and *P. gallinaceum* appear to be respectively rather less and rather more sensitive to proguanil than ours. The morphological changes in the parasites after being treated with (VI; R = Cl) were similar to those observed after treatment with proguanil or sulphadiazine; instead of dividing normally, the chromatin of the schizonts becomes greatly subdivided and there is no formation of merozoites. Furthermore, (VI; R = Cl) readily cleared the blood of mice infected with *P. berghei*, whereas proguanil only does so at the maximum tolerated dose. The activity of (VI; R = Cl) against *P. berghei*, in the mouse (at 0·3 mg./20 g., intraperitoneally, once daily × 4) was not antagonised by *p*-aminobenzoic acid (10 mg./20 g., *per os*, b.i.d. × 4), or by pteroylglutamic acid (2 mg., similarly), and it was equally active against normal and sulphadiazine-resistant strains of the parasite. The activity of (VI; R = Cl) against *P. gallinaceum* in the chick (at 2 mg./100 g., *per os*, b.i.d. × 3½) was likewise not antagonised by *p*-aminobenzoic acid (10 mg., similarly) or by pteroylglutamic acid (3 mg., similarly). Against *P. berghei*, (VI; R = H), which was rather more toxic to mice, showed a trace of activity, and against *P. gallinaceum* in the chick it was active at a minimum effective dose of 4 mg./100 g., *per os*, b.i.d. × 3½. None of the other compounds described, including the 6-chloro-derivative of (VI; R = H), showed any activity against either parasite with the exception of *p*-chlorophenylguanidinomethyleneacetonitrile, which showed a trace of activity against *P. berghei* in the mouse. As active compounds of the 2 : 4-diaminopyrimidine type are also active against proguanil-resistant laboratory strains (Falco *et al.*, *loc. cit.*), their mode of action must be complementary to that of the activated metabolite of proguanil.

Experimental.

α-(*Methoxymethylene*)*phenylacetonitrile* (VII*b*; R = Me).—(*a*) An ice-cold solution of diazomethane (from 25 g. of nitrosomethylurea) in ether (200 c.c.) was added in portions with swirling to a suspension of α-formylphenylacetonitrile (14·5 g.) in ether (100 c.c.) at 0°. The formyl compound dissolved with evolution of nitrogen, and the solution rapidly deposited colourless fibres. After being kept at 0° (2 hours) and at room temperature (overnight), the solid (1·82 g.) was collected and washed with ether (20 c.c.). Recrystallisation from aqueous alcohol yielded long colourless threads of *βγ-epoxy-α-phenylbutyronitrile*, m. p. 176—178° (Found: C, 75·3; H, 5·3; N, 8·9; OMe, 0. $C_{10}H_9ON$ requires C, 75·4; H, 5·7; N, 8·8%). Removal of the ether and excess of diazomethane by distillation, and trituration of the residue with ethanol–light petroleum gave α-(*methoxymethylene*)*phenylacetonitrile* (3·4 g.), which separated from light petroleum in lustrous, colourless plates, m. p. 67—68° (Found: C, 75·3; H, 6·0; N, 9·1; OMe, 19·0. $C_{10}H_9ON$ requires C, 75·4; H, 5·7; N, 8·8; OMe, 19·5%). Extraction of the evaporated mother-liquors with boiling light petroleum yielded a further quantity of the enol methyl ether (1·2 g.; total yield, 4·6 g., 29%).

The epoxide showed no signs of reacting with Brady's reagent in the usual manner. It (250 mg.) was refluxed with 2N-potassium hydroxide (5 c.c.) for 5 hours and the solution, when diluted with water, yielded only a trace of brown gum to ether. Acidification and extraction with ether gave phenylacetic acid (165 mg.), m. p. after recrystallisation from light petroleum, and mixed m. p., 75·5—76·5°.

(*b*) Anhydrous potassium carbonate (14 g.), followed by methyl iodide (21·3 g.), was added to a solution of formylphenylacetonitrile (14·5 g.) in dry acetone, and the mixture was refluxed for 8 hours. Ether (150 c.c.) was added, and the solution filtered and evaporated. The product was distributed between ether and 0·5N-sodium hydroxide, and the ethereal layer was dried and evaporated, giving a residue (12·9 g.) which crystallised in the refrigerator. Fractionation gave: (i) oil (3·17 g.), b. p. up to 110°/0·5 mm.; (ii) oil (4·24 g.), b. p. 110—112°/0·5 mm.; (iii) oil (3·89 g.), b. p. 112°/0·5 mm.; (iv) oil (0·45 g.), which rapidly crystallised, b. p. 112—114°/0·5 mm.; (v) still residue which crystallised and gave the enol ether (1·0 g.), m. p. 67—68°, on crystallisation from light petroleum. Fraction (iii) did not crystallise on nucleation with fraction (iv); (ii), (iii), and (iv) were bulked and then had n_D^{20} 1·5786 (Found: OMe, 18·8%).

α-(iso*Butoxymethylene*)*phenylacetonitrile* (VII*b*; R = Bu^i).—A mixture of formylphenylacetonitrile (7·25 g.), *iso*butanol (7·4 g.), and toluene-*p*-sulphonic acid (0·1 g.) in benzene was boiled under reflux for 20 hours in a conventional Dean and Stark apparatus. The cooled solution was washed with N-sodium hydroxide solution (50 c.c.) and with water, and dried ($CaCl_2$). Fractionation afforded α-(iso*butoxymethylene*)-*phenylacetonitrile* as a colourless viscous oil (9·1 g., 90%), b. p. 119—120°/0·1 mm., n_D^{22} 1·5445 (Found: C, 77·6; H, 7·7; N, 7·2. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%).

2 : 4-*Diamino-5-phenylpyrimidine* (VI; R = H).—(*a*) Guanidine nitrate (1·83 g.), followed by methoxymethylenephenylacetonitrile (1·59 g.), was added to a solution of sodium ethoxide (from 0·46 g. of sodium) in absolute alcohol (50 c.c.), and the mixture was refluxed for 5 hours. The residue after removal of the solvent under reduced pressure was shaken with ether (50 c.c.) and water (50 c.c.). The crystalline product (0·95 g.) was filtered off and a further quantity (0·61 g.; total yield, 1·56 g., 84%) was recovered from the ether. Crystallisation from benzene afforded colourless laths of 2 : 4-*diamino-5-phenylpyrimidine*, m. p. 162·5—163·5° (Found: C, 64·3; H, 5·4; N, 30·2. $C_{10}H_{10}N_4$ requires C, 64·3; H, 5·4; N, 30·1%).

(*b*) Under precisely similar conditions guanidine nitrate and *iso*butoxymethylenephenylacetonitrile afforded an identical product in 69% yield.

(*c*) A suspension of 2 : 4-diamino-6-chloro-5-phenylpyrimidine (1 g.) (see below) in ethanol (120 c.c.) containing 2N-potassium hydroxide (3 c.c.) was shaken with 2% palladised strontium carbonate (0·5 g.) in hydrogen at atmospheric pressure. The theoretical volume of hydrogen was absorbed in 8 hours and the filtered solution was evaporated to dryness. The residue was extracted with boiling benzene (100 c.c.), and the filtered extract was concentrated to small bulk (15 c.c.). On cooling, 2 : 4-diamino-5-phenylpyrimidine (0·77 g., 91%) separated, m. p. 162—163°, alone and in admixture with the products isolated in experiments (*a*) and (*b*) (above).

α-(*Guanidinomethylene*)*phenylacetonitrile* (IX).—Dry, powdered guanidine nitrate (6·7 g.), followed by formylphenylacetonitrile (7·25 g.), was added to a solution of sodium ethoxide (from 1·4 g. of sodium) in absolute alcohol (100 c.c.), and the solution was boiled under reflux for 8 hours. After removal of the alcohol under reduced pressure, the solid product was distributed between water (100 c.c.) and a large volume of ether. Evaporation of the dried ethereal solution and crystallisation of the residue from benzene gave colourless needles (3·05 g.) of α-(*guanidinomethylene*)*phenylacetonitrile*, m. p. 138·5—139·5° (Found: C, 64·4; H, 5·3; N, 29·5. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%).

The substance (500 mg.) was boiled under reflux with 0·5N-hydrochloric acid (25 c.c.) for 1½ hours. The cooled solution was basified with 2N-sodium hydroxide and thoroughly extracted with ether. Removal of the ether and crystallisation of the residue from methanol–ethyl acetate afforded colourless needles (345 mg.) of phenylacetylguanidine, m. p. 170—171°, alone and in admixture with an authentic specimen prepared from ethyl phenylacetate and guanidine (Simons and Weaver, U.S.P. 2,408,694) (Found: C, 61·3; H, 6·3; N, 23·7. Calc. for $C_9H_{11}ON_3$: C, 60·9; H, 6·3; N, 23·8%). Prolonged hydrolysis (17 hours) under the same conditions yielded phenylacetic acid, m. p. and mixed m. p. 75—76°.

Attempts to prepare (IX) from aminomethylenephenylacetonitrile (Davies and Piggott, *J.*, 1945, 351) and either *S*-methyl*iso*thiourea or *O*-methyl*iso*urea under standard conditions were abortive, the aminomethylenephenylacetonitrile being recovered unchanged.

2 : 4 : 6-*Trichloro-5-phenylpyrimidine*.—5-Phenylbarbituric acid (2·04 g.) (Lund, *Chem. Zentr.*, 1936, I, 2095) was added to a mixture of phosphoryl chloride (7·7 g.) and redistilled dimethylaniline (2·7 g.).

After refluxing for 20 minutes, the red solution was poured on crushed ice (250 g.) and extracted with ether. Removal of the ether from the dried extract gave a buff-coloured solid (2·55 g.). Sublimation at 170—180° (bath-temp.)/15 mm. gave two colourless fractions : (i) (1·75 g.) m. p. 153—158°, and (ii) (0·27 g.) m. p. 157—162°, subliming more slowly. Recrystallisation of (i) from alcohol afforded large plates of 2 : 4 : 6-*trichloro-5-phenylpyrimidine*, m. p. 159—160° (Found : C, 46·5; H, 2·1; N, 10·8; Cl, 39·9. $C_{10}H_5N_2Cl_3$ requires C, 46·3; H, 1·9; N, 10·8; Cl, 41·1%). Recrystallisation of (ii) from alcohol gave colourless needles of 4 : 6-*dichloro-2-methylanilino-5-phenylpyrimidine*, m. p. 167—167·5° (Found : N, 12·4; Cl, 21·4. $C_{17}H_{13}N_3Cl_2$ requires N, 12·7; Cl, 21·5%).

Omission of the dimethylaniline and prolonged boiling with phosphoryl chloride gave only a trace of the desired trichlorophenylpyrimidine, and substitution of quinoline for dimethylaniline gave a 15% yield of the trichloro-compound. The awkward separation of trichlorophenylpyrimidine and dichloromethylanilinophenylpyrimidine could be avoided by using the mixture directly (following experiment).

2 : 4-*Diamino-6-chloro-5-phenylpyrimidine*.—2 : 4 : 6-Trichloro-5-phenylpyrimidine (2·1 g.) and ethanolic ammonia (70 c.c.; saturated at 0°) were heated at 120° for 6 hours in a stainless-steel tube. After being kept at 0° overnight, the solution and solid were washed out with ethanol, and the mixture was taken to dryness under reduced pressure. The colourless residue was shaken with a mixture of ether (50 c.c.) and water (100 c.c.) and filtered off. Recrystallisation of the residue from alcohol gave colourless plates (1·55 g., 87%) of 2 : 4-*diamino-6-chloro-5-phenylpyrimidine*, m. p. 244—245° (Found : C, 54·5; H, 4·3; N, 25·5. $C_{10}H_9N_4Cl$ requires C, 54·4; H, 4·1; N, 25·4%). The compound was practically insoluble in water, ether, or chloroform.

Alternatively, the mixture of 2 : 4 : 6-trichloro-5-phenylpyrimidine and 4 : 6-dichloro-2-methylanilino-5-phenylpyrimidine was ammonolysed and the 4-*amino-6-chloro-2-methylanilino-5-phenylpyrimidine*, formed from the latter, was readily separated from the 2 : 4-diamino-6-chloro-5-phenylpyrimidine by taking advantage of the sparing solubility of the latter in cold ethanol; it separated from ethanol in colourless needles, m. p. 166—167° (Found : C, 65·9; H, 4·8; N, 18·3. $C_{17}H_{13}N_4Cl$ requires C, 65·7; H, 4·8; N, 18·0%).

p-*Aminophenylacetonitrile*.—A suspension of *p*-nitrophenylacetonitrile (100 g.) (*Org. Synth.*, Coll. Vol. I, 1932, p. 389) in a mixture of ethyl acetate (450 c.c.) and ethanol (150 c.c.) was shaken with 2% palladised strontium carbonate (1 g.) in hydrogen at a pressure of 10 atm. The theoretical volume of hydrogen was absorbed in 24 hours and the filtered solution was evaporated to dryness. The addition of 5N-hydrochloric acid to a stirred solution of the residue in chloroform (250 c.c.) afforded the colourless hydrochloride (91·5 g., 88%) of *p*-aminophenylacetonitrile, m. p. 228°, which was collected, washed, and dried. The hydrochloride crystallised from aqueous alcohol in plates, m. p. 229—231°. Czumpelik (*Ber.*, 1870, **3**, 474) describes this substance as crystallising in plates but records no m. p.

p-*Chlorophenyl-α-formylacetonitrile*.—*p*-Chlorophenylacetonitrile (50·5 g.), prepared in 68% yield from the foregoing amine by the method of Davies, Johnson, and Piggott (*J.*, 1945, 352), in absolute alcohol (75 c.c.) was added to sodium ethoxide (from 11·5 g. of sodium) in absolute alcohol (500 c.c.). The stirred solution was cooled in melting ice while ethyl formate (50 g.) was added dropwise. The mixture was then stirred at room temperature for 4 hours and refluxed finally for an hour before removal of most of the solvent under reduced pressure. The residue was taken up in water (750 c.c.) and extracted with ether. Acidification of the aqueous alkaline layer, extraction with ether, and evaporation of the dried extract yielded *p*-chlorophenyl-α-formylacetonitrile (53·8 g., 90%), which separated from aqueous alcohol or from ethyl acetate–light petroleum in colourless plates, m. p. 163—164°. Walther and Hirschberg (*J. pr. Chem.*, 1903, **67**, 393) record m. p. 159—161°.

α-iso*Butoxymethylene-p-chlorophenylacetonitrile*.—A solution of *p*-chlorophenylformylacetonitrile (20 g.), *iso*butanol (20 g.), and toluene-*p*-sulphonic acid (0·1 g.) in benzene (250 c.c.) was boiled under reflux for 16 hours in the Dean and Stark apparatus, cooled, and washed with N-sodium hydroxide (100 c.c.). Unchanged starting material (2·8 g., 14%) was recovered by acidifying the alkaline washings. Fractionation of the benzene solution yielded α-iso*butoxymethylene-p-chlorophenylacetonitrile* as a colourless oil (20·3 g., 78%), b. p. 139—141°/0·1 mm. On storage at 0° the product partly crystallised; the oil was drained off and recrystallisation of the solid from light petroleum afforded colourless, flattened prisms (5·1 g.), m. p. 62—63° (Found : C, 66·4; H, 6·0; N, 6·2. $C_{13}H_{14}ONCl$ requires C, 66·2; H, 6·0; N, 5·9%).

2 : 4-*Diamino-5-p-chlorophenylpyrimidine* (VI; R = Cl).—*iso*Butoxymethylene-*p*-chlorophenylacetonitrile (20·1 g., mixed stereoisomerides) was added to a solution of sodium ethoxide (from 2·35 g. of sodium) in absolute ethanol (200 c.c.), followed by guanidine nitrate (11·5 g.). A reddish-brown colour appeared on mixing and the solution was boiled under reflux for 21 hours. The solvent was removed and the residue shaken with a mixture of ether (100 c.c.) and water (200 c.c.), the solid product (13·9 g., 74%) being collected. Recrystallisation from *n*-butanol afforded colourless needles of 2 : 4-*diamino-5-p-chlorophenylpyrimidine*, m. p. 188—190° (Found : C, 54·7; H, 4·4; N, 25·8. $C_{10}H_9N_4Cl$ requires C, 54·4; H, 4·1; N, 25·4%). In another experiment the product separated from the same solvent in colourless plates, m. p. 195—196°, alone and in admixture with the form of m. p. 188—190°; either form could be converted into the other by seeding. The separate use of either the solid or the liquid fractions of the enol *iso*butyl ether afforded similar yields. No other product could be isolated.

p-*Chlorophenyl-α-(guanidinomethylene)acetonitrile*.—*p*-Chlorophenylformylacetonitrile (9 g.), followed by guanidine nitrate (9·15 g.), was added to sodium ethoxide (from 2·3 g. of sodium) in absolute alcohol (150 c.c.), and the mixture was boiled under reflux before being worked up in the manner described for the phenyl analogue (IX). On crystallisation from *n*-butanol the product (3·85 g.) afforded colourless prisms of p-*chlorophenyl-α-(guanidinomethylene)acetonitrile*, m. p. 206—207° (Found : C, 54·8; H, 4·3; N, 25·5. $C_{10}H_9N_4Cl$ requires C, 54·4; H, 4·1; N, 25·4%).

6-*Amino*-4-*p-chloroanilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-s-*triazine* (III).—The following method afforded much better yields than those recorded by Birtwell *et al.* (*J.*, 1948, 1655), who used a longer period of heating, or by Crounse (*J. Org. Chem.*, 1951, **16**, 500). A mixture of *p*-chlorophenyldiguanide (10·8 g.), piperidine (1 c.c.), and acetone (45 c.c.) was boiled under reflux for ½ an hour, kept at 37° overnight, and again refluxed for 2 hours. The solution was then treated with charcoal, filtered, and washed through with acetone. Concentration (to 35 c.c.) and addition of water (140 c.c.) precipitated a rapidly crystallising oil. The solid was collected after 1 hour at 0°, and recrystallisation from aqueous alcohol gave colourless prisms (10·7 g.), m. p. 129·5—131·5°.

The same product was obtained by boiling a mixture of *p*-chlorophenyldiguanide (9 g.), acetone (6·5 c.c.), and acetic acid (15 c.c.) under reflux for 24 hours. Removal of the solvent under reduced pressure gave a product which could not be made to crystallise satisfactorily. Treatment with 5N-hydrochloric acid (20 c.c.), followed by evaporation and crystallisation of the residue from alcohol–ether, gave the crude hydrochloride (4·4 g.), yielding the free base (3·25 g.) on treatment in hot aqueous solution with excess of concentrated aqueous ammonia.

The *dihydrochloride* separated from methanol–ethyl acetate in hard clumps of colourless prisms, m. p. 190° (decomp.) (Found: C, 40·1; H, 4·6; N, 21·5. $C_{11}H_{14}N_6Cl,2HCl$ requires C, 40·7; H, 4·9; N, 21·6%).

The authors are indebted to Mr. R. J. Clark for technical assistance.

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[*Received, August 22nd,* 1951.]

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760. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part VIII.* 3 : 3′-Dimethylnaphthidine as Indicator in the Titration of Cadmium, Calcium, and Indium with Ferrocyanide.†*

By R. Belcher, A. J. Nutten, and W. I. Stephen.

Cadmium, calcium, and indium can be titrated with ferrocyanide, 3 : 3′-dimethylnaphthidine being used as indicator. Naphthidine, *o*-dianisidine, and *NN*′-diphenylbenzidine are less satisfactory in these titrations.

It has been shown that naphthidine (Belcher and Nutten, *J.*, 1951, 548) and 3 : 3′-dimethylnaphthidine (4 : 4′-diamino-3 : 3′-dimethyl-1 : 1′-dinaphthyl) (Belcher, Nutten, and Stephen, *J.*, 1951, 1520) can be used as internal indicators in the titration of zinc with ferrocyanide. The present paper describes the behaviour of these indicators in the titration of three other metals which form insoluble ferrocyanides, namely, cadmium, calcium, and indium.

Titration of Cadmium.—When the titration was carried out in neutral solution in the presence of ammonium sulphate, both indicators gave very sharp end-points. Both direct titration with standard ferrocyanide, and addition of a known excess followed by back-titration with a standard cadmium solution, gave satisfactory results. Our own preference is, however, for the direct titration method.

Results included in the following table apply to both naphthidine and 3 : 3′-dimethylnaphthidine, similar figures being obtained for both indicators. In all our experiments, the volume of the solution to be titrated was 40 ml. No indicator correction was found to be necessary.

0·05M-Cd, ml.	10% $(NH_4)_2SO_4$, ml.	0·05M-$K_4Fe(CN)_6$, ml.	Ratio $Cd/K_4Fe(CN)_6$	0·01M-Cd, ml.	10% $(NH_4)_2SO_4$, ml.	0·01M-$K_4Fe(CN)_6$, ml.	Ratio $Cd/K_4Fe(CN)_6$
5	10	4·00, 4·02, 4·00	1·25, 1·24, 1·25	1	10	0·82, 0·80	1·22, 1·25
10	10	8·02, 8·00, 8·00	1·25, 1·25, 1·25	2	10	1·60, 1·62	1·25, 1·24
15	10	12·03, 12·04, 12·00	1·25, 1·25, 1·25	4	10	3·22, 3·23	1·24, 1·24
20	10	16·00, 16·00, 16·03	1·25, 1·25, 1·25	5	10	4·00, 3·98	1·25, 1·26
				10	10	8·03, 8·02	1·25, 1·25

* Part VII, *J.*, 1951, 1520. † Read, in abstract, at 12th International Congress of Pure and Applied Chemistry, New York, September, 1951.

In acid solution low results were obtained, as shown below, and the titration had to be done very slowly, because the colour of the indicator faded and then reappeared throughout the titration.

0·05M-Cd, ml.	5	5	5	5	5	5	5
2N-H_2SO_4, ml.	20	10	8	6	4	2	1
10% $(NH_4)_2SO_4$, ml.	10	10	10	10	10	10	10
Acid concn., N.	1	0·5	0·4	0·3	0·2	0·1	0·05
0·05M-$K_4Fe(CN)_6$, ml.	3·72	3·80	3·84	3·84	3·88	3·94	3·99

An end-point could not be obtained when ammonium salts were absent: either the chloride or the sulphate was satisfactory, but, when large amounts of chloride were present, slightly high results were obtained. The maximum amount of ammonium chloride which could be tolerated was 0·2 g. Amounts of ammonium sulphate ranging between 0·5 and 2·0 g. could be added, but below 0·5 g. the end-points were unsatisfactory and slightly high results were obtained; in most of our experiments about 1 g. was added. The following results are typical of both indicators.

0·05M-Cd, ml.	10% $(NH_4)_2SO_4$, ml.	0·05M-$K_4Fe(CN)_6$, ml.	0·05M-Cd, ml.	10% NH_4Cl, ml.	0·05M-$K_4Fe(CN)_6$, ml.
5	2	4·3, 4·34	5	2	4·02, 4·00
5	3	4·25, 4·22	5	4	4·07, 4·06
5	4	4·06, 4·05	5	5	4·12, 4·15
5	5	4·02, 4·00	5	10	4·11, 4·15
5	10	4·00, 4·01	5	20	4·22, 4·24
5	15	4·00, 4·00			
5	20	4·02, 4·00			

Obviously, all metals which form insoluble ferrocyanides will interfere. The only interferences we examined were those of barium and strontium. In the absence of sulphate ions high results were obtained, but, when ammonium sulphate was added barium and strontium sulphates were precipitated and no longer interfered.

Amounts of cadmium ranging from 1 ml. of a 0·1M-solution to 20 ml. of a 0·05M-solution (*i.e.*, 1·12—112·41 mg. of Cd) were titrated. From the titration relationships the precipitate appears to have the composition $Cd_2K_2[Fe(CN)_6]_2$, in agreement with the formula assigned to it by Wyrouboff (*Ann. Chim.*, 1870, **21**, 270).

o-Dianisidine and *NN'*-diphenylbenzidine were also tried as indicators in the titration. The respective merits of all four indicators can be summarised as follows:

Indicator	Comment
3 : 3'-Dimethylnaphthidine	Very good. End-points sharp at all concentrations
Naphthidine	Good. End-points less sharp than with 3 : 3'-dimethylnaphthidine
o-Dianisidine	Almost as good as naphthidine
NN'-Diphenylbenzidine	Very poor. End-points difficult to detect

Titration of Calcium.—When calcium was titrated in neutral aqueous solution, end-points could not be obtained whether ammonium salts were present or not. When, however, ethyl alcohol was added to the solution, satisfactory end-points were obtained, owing to the decreased solubility of the calcium potassium ferrocyanide: the initial concentration should be 85—90% of ethyl alcohol, and 80—85% at the end of the titration. A larger amount of potassium ferricyanide is required than in other titrations of this type, but no correction is necessary.

In solutions of high acid concentration end-points with naphthidine and 3 : 3'-dimethylnaphthidine could not be obtained, although an acidity of 0·05N. with respect to hydrochloric acid could be tolerated.

Amounts of calcium ranging from 1 ml. of 0·01M-solution to 5 ml. of 0·05M-solution (0·4—10·02 mg. of Ca) were titrated satisfactorily. From the titration relationships the formula of the precipitate corresponds to $CaK_2[Fe(CN)_6]$. Results with 3 : 3'-dimethylnaphthidine and naphthidine are given below, the results obtained for both indicators being comparable.

0·05M-Ca, ml.	EtOH, ml.	0·05M-$K_4Fe(CN)_6$, ml.	Ratio $Ca/K_4Fe(CN)_6$	0·01M-Ca, ml.	EtOH, ml.	0·01M-$K_4Fe(CN)_6$, ml.	Ratio $Ca/K_4Fe(CN)_6$
2	35	1·98, 2·00	1·01, 1·00	1	35	1·02, 1·00	0·98, 1·00
4	35	4·00, 4·02	1·00, 0·99	2	35	2·00, 1·98	1·00, 1·01
5	35	5·00, 5·00	1·00, 1·00	4	35	4·00, 4·00	1·00, 1·00
				5	35	5·00, 5·00	1·00, 1·00

The behaviour of the other alkaline-earth metals and of magnesium was also studied. Barium could be titrated by the same procedure, but end-points could not be obtained with strontium and magnesium. When calcium was titrated, however, in the presence of the last two metals, high results were obtained, possibly owing to the formation of other complex insoluble ferrocyanides in which magnesium and strontium were incorporated.

The same four indicators were examined in this titration and their behaviour can be summarised as follows:

Indicator	Comment
3 : 3′-Dimethylnaphthidine	Satisfactory. End-point very sharp
o-Dianisidine	Poor. End-point difficult to detect
Naphthidine	Slightly poorer than *o*-dianisidine. End-point difficult to detect
NN′-Diphenylbenzidine	Very poor. No end-point

Although the end-points with 3 : 3′-dimethylnaphthidine are easily detected, they are not so sharp as those obtained in the cadmium titration.

Titration of Indium.—Two methods have been described previously for the titration of indium with ferrocyanide. In one, the titration is effected in acetic acid solution with *NN′*-diphenylbenzidine as indicator (Hope, Ross, and Skelley, *Ind. Eng. Chem. Anal.*, 1936, **8**, 51), and in the other, the titration is effected in hydrochloric acid solution and the end-points are determined potentiometrically (Bray and Kirchmann, *J. Amer. Chem. Soc.*, 1927, **49**, 2739). The latter workers state that the composition of the indium salt formed is $In_3K[Fe(CN)_6]_4$; but presumably under the conditions of Hope, Ross, and Skelley, the precipitate is of uncertain composition, for the ferrocyanide solution must be standardised against pure indium under the conditions of an actual determination.

In the present investigation it was found that titration could be done in acid solution in the presence of ammonium sulphate or ethyl alcohol, but the ratio In : $Fe(CN)_6$ was 5 : 4·2 instead of 5 : 4 as would be expected from the above formula. In acetic acid solution the end-points with naphthidine, 3 : 3′-dimethylnaphthidine, and *o*-dianisidine were poor and variable, the colours of the first two indicators fading throughout the titration; however, 3 : 3′-dimethylnaphthidine gave much better end-points than *NN′*-diphenylbenzidine.

In neutral solution excellent end-points were obtained and the ratio In : $Fe(CN)_6$ was exactly 5 : 4, corresponding to the above formula. Direct titration was possible, but it was preferable to add an excess of ferrocyanide solution and to back-titrate with a standard indium solution. Amounts of indium varying from 1 ml. of 0·01M-solution to 20 ml. of 0·05M-solution (1·15—114·8 mg. of In) were titrated satisfactorily. Results with 3 : 3′-dimethylnaphthidine are included in the following table.

0·05M-In, ml.	0·05M-$K_4Fe(CN)_6$, ml.	Back-titrn. : 0·05M-In, ml.	Ratio In/$K_4Fe(CN)_6$	0·01M-In, ml.	0·01M-$K_4Fe(CN)_6$, ml.	Back-titrn. : 0·01M-In, ml.	Ratio In/$K_4Fe(CN)_6$
5	5·0, 6·0	1·24, 2·52	1·25, 1·25	1	1·5, 1·0	0·90, 0·25	1·27, 1·25
10	10·0, 15·0	2·50, 8·72	1·25, 1·25	2	2·0, 3·0	0·48, 1·72	1·24, 1·24
15	15·0, 15·0	3·77, 3·73	1·25, 1·25	4	4·0, 6·0	1·00, 3·47	1·25, 1·25
20	20·0, 25·0	5·10, 11·30	1·26, 1·25	5	5·0, 5·5	1·26, 1·92	1·25, 1·26
				10	10·0, 12·0	2·52, 4·97	1·25, 1·25

Experimental.

Solutions required.—Cadmium, 0·05M., 0·01M. The solutions were prepared by dissolving "AnalaR" cadmium sulphate in distilled water, and standardised by gravimetric determination of the cadmium with 8-hydroxyquinoline.

Calcium, 0·05M., 0·01M. These were prepared by dissolving "AnalaR" calcium carbonate in 2N-hydrochloric acid and neutralising them with 1N-sodium hydroxide; they were standardised by gravimetric determination of the calcium as oxalate.

Indium, 0·05M., 0·01M. Pure indium metal was dissolved in 11N-hydrochloric acid, the solution evaporated to dryness, and the resulting chloride dissolved in distilled water.

Potassium ferrocyanide, 0·05M., 0·01M. "AnalaR" Potassium ferrocyanide trihydrate was dissolved in distilled water containing 0·2 g. of sodium carbonate per litre. The solutions were standardised by titration with a standard zinc solution, 3 : 3′-dimethylnaphthidine being used as indicator.

Potassium ferricyanide. 1% Solution was prepared fresh each day and kept in a dark bottle.

Ammonium sulphate. 10% Solution.

Indicator: 3 : 3′-*dimethylnaphthidine.* Prepared by dissolving, with warming, 1 g. of the compound in 100 ml. of glacial acetic acid.

Titration of Cadmium.—10 Ml. of 10% ammonium sulphate were added to 1—10 ml. of neutral cadmium solution and the volume adjusted to 40 ml. with distilled water. Two drops of 1% potassium

ferricyanide and 2 drops of indicator were added, and the solution was titrated with potassium ferrocyanide solution until the colour changed from red-violet to white.

Titration of Calcium.—35 Ml. of ethyl alcohol were added to 1—5 ml. of neutral calcium solution, and the volume adjusted to 40 ml. with distilled water. Further procedure was as above, but the solution was titrated moderately rapidly until a slight fading of the indicator occurred, and then dropwise to a permanent change from pink to pale yellow.

Titration of Indium.—Sufficient distilled water was added to 1—20 ml. of neutral indium solution to give a volume of 40 ml. and 4 drops of potassium ferricyanide solution and 2 drops of indicator were added. Potassium ferrocyanide solution was added in excess, and the solution back-titrated with a standard indium solution until its colour changed from grey-white to pink-violet.

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[*Received, July 16th*, 1951.]

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761. *The Chemistry of Subterranean Clover. Part I. Isolation of Formononetin and Genistein.*

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Two *iso*flavones, formononetin (7-hydroxy-4′-methoxy*iso*flavone) and genistein (5 : 7 : 4′-trihydroxy*iso*flavone) have been isolated from the " chloroplast fraction " of subterranean clover, and genistein has been shown to be mainly responsible for its œstrogenic activity.

THE œstrogenic properties of the Dwalganup strain of subterranean clover (*Trifolium subterraneum* L.) are of great importance to sheep breeding in the drier areas of Western Australia, and have already been the subject of considerable investigation (Bennetts, Underwood, and Shier, *Austral. Vet. J.*, 1946, **22**, 2; Bennetts, *ibid.*, p. 70; 1947, **23**, 10; Curnow, Robinson, and Underwood, *Austral. J. Exp. Biol. Med. Sci.*, 1948, **26**, 171; East, Underwood, and Bennetts, *ibid.*, 1949, **27**, 105; Robinson, *ibid.*, p. 297). Concentration of the œstrogen into the " chloroplast fraction " of plants was effected by Curnow, Legg, and Simpson (*Biochem. J.*, 1950, **46**, xix), and examination of concentrated extracts prepared from this material (Curnow, Thesis, Univ. London, 1950; Beck and Braden, in the press) has shown that the œstrogen is phenolic, but its infra-red absorption spectrum (Curnow, private communication) and comparison of its partition coefficients with those of known steroid œstrogens failed to identify it.

In the present investigation, the " chloroplast fraction " prepared from a large quantity of clover was extracted with alcohol and, after removal of the fats from this extract with light petroleum, crystals separated from a concentrated alcoholic solution. These were identified as formononetin (7-hydroxy-4′-methoxy*iso*flavone) from the analyses and melting points of the compound and some of its derivatives, and by comparison of the degradation product, 2 : 4-dihydroxyphenyl 4′-methoxybenzyl ketone, with a synthetic specimen (Baker and Eastwood, *J.*, 1929, 2897).

Formononetin was previously obtained from *Ononis spinosa* L. where it occurs as the glycoside ononin (Hlasiwetz, *J. prakt. Chem.*, 1855, **65**, 419; Wessely and Lechner, *Sitzungsber. Akad. Wiss. Wien*, 1930, **139**, II*b*, 1061; Wessely, Lechner, and Dinjaski, *ibid.*, 1933, **142**, II*b*, 411).

From the material in the mother-liquor, chromatography on alumina, followed by crystallisation from aqueous alcohol, yielded, in addition to a further quantity of formononetin, a considerable quantity of genistein (5 : 7 : 4′-trihydroxy*iso*flavone) which was identified in a similar manner, and also by comparison with a synthetic specimen. This was prepared by condensing 2-hydroxy-4 : 6-dimethoxyphenyl 4′-methoxybenzyl ketone (Badcock, Cavill, Robertson, and Whalley, *J.*, 1950, 2965) with ethyl formate to give 5 : 7 : 4′-trimethoxy*iso*flavone, which was demethylated to genistein.

Genistein has been reported as glycosides in *Genista tinctoria* L. (Perkin and Newbury, *J.*, 1899, **75**, 830), *Soja hispida* L. (Walz, *Annalen*, 1931, **489**, 118), and *Sophora japonica* L. (Charaux and Rabaté, *J. Pharm. Chim.*, 1935, [viii], **21**, 546) and was synthesised by Baker and Robinson (*J.*, 1928, 3115).

Biological tests on natural and synthetic genistein have demonstrated its œstrogenic activity and, although this is low (about 10^{-3} that of œstrone), the amount present (2 mg. per 100 g. of fresh clover) indicates that it must be the principal œstrogen in the clover.

Experimental.

M. p.s are corrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Dr. W. Zimmermann, Melbourne.

Preparation of "Chloroplast Fraction."—Freshly mown subterranean clover (Dwalganup strain; 4020 kg.), collected in 1950 at the period of maximum growth (October), which previous workers had found to be the time of maximum œstrogenic activity, was macerated in 700-kg. batches in a hammer mill and pressed in a hydraulic press. In this way 1500 l. of juice were obtained (corresponding to 43% of the total water content of the clover); they were heated to 90° as rapidly as possible (90-l. batches, with four 2-kw. immersion heaters). After being left for 12 hours to cool, the supernatant liquid was siphoned off and the sludge filtered on Whatman No. 4 filter papers in Büchner funnels, dried at 100° to 7—10% moisture content, and powdered (15 kg.).

Extraction of "Chloroplast Fraction."—Extraction of the "chloroplast fraction" (4·4 kg.) by percolation with alcohol (24 l.) at room temperature gave, on evaporation of the solvent, 473 g. of extract. Exhaustive extraction of this with boiling light petroleum (b. p. 40—60°) removed 118 g. of material with negligible œstrogenic activity, and the residue was dissolved in alcohol (320 ml.) and poured slowly into ether (2880 ml.), which was cooled in ice and stirred constantly. After being kept at room temperature overnight, the insoluble residue, which showed negligible œstrogenic acitivty, was separated and the solution evaporated to dryness (100 g.).

Isolation of Formononetin.—The above material (100 g.) was extracted five times with light petroleum (100 ml.), and the residue (89·5 g.) dissolved in the minimum amount of boiling alcohol, treated with charcoal, and filtered. On cooling, formononetin separated (5·2 g.). It was readily purified by solution in cold, very dilute aqueous sodium hydroxide, precipitation with acid, and crystallisation, or by chromatography on alumina. It separated from alcohol in long, colourless needles, curved when impure, m. p. 258° (Found: C, 71·8, 71·6; H, 4·8, 4·6; OMe, 10·6%; *M*, 291. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5; OMe, 11·6%; *M*, 268). Light absorption in ethanol: $\varepsilon_{max.}$ 27,440 at 2500 Å; $\varepsilon_{max.}$ 11,240 at 3000 Å. Wessely, Lechner, and Dinjaski (*loc. cit.*) record m. p. 259°.

Acetylformononetin. Formononetin (1·0 g.) and acetic anhydride (5 ml.) were refluxed for 15 minutes and the product isolated and washed with water and crystallised from alcohol. It formed colourless needles, m. p. 171—172° (0·8 g.) (Found: C, 69·2; H, 4·7; $CH_3{\cdot}CO$, 27·7. Calc. for $C_{18}H_{14}O_5$: C, 69·7; H, 4·5; $CH_3{\cdot}CO$ and $H{\cdot}CO_2H$ calc. as $CH_3{\cdot}CO$, 27·7%). Wessely, Lechner, and Dinjaski (*loc. cit.*) and Mahal, Rai, and Venkataraman (*J.*, 1934, 1769) record m. p. 170°.

Propionylformononetin. Formononetin (1·0 g.) and propionic anhydride (5 ml.) were refluxed for 15 minutes and the product isolated and washed with water. *Propionylformononetin* formed long, colourless needles, m. p. 132°, from alcohol (Found: C, 70·1; H, 4·8. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%).

7 : 4′-*Dimethoxyisoflavone.*—Addition of excess of diazomethane in ether to a solution of formononetin in alcohol formed 7 : 4′-dimethoxy*iso*flavone, rosettes of needles, m. p. 162—163°, from alcohol or benzene (Found: C, 72·8; H, 4·9; OMe, 19·7, 19·9%; *M*, 256. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0; OMe, 22·0%; *M*, 282). Wessely, Lechner, and Dinjaski (*loc. cit.*) record m. p. 163°.

Daidzein.—Formononetin (0·5 g.) was refluxed with hydriodic acid (*d* 1·7; 10 ml.) for 2 hours, and the mixture poured into water and decolorised with sulphur dioxide. The daidzein obtained (0·44 g.) formed colourless needles, m. p. 325° (decomp.), from alcohol. It gave no colour with ferric chloride. Wessely and Lechner (*Ber.*, 1933, **66**, 685) record m. p. 323°.

2 : 4-*Dihydroxyphenyl* 4′-*Methoxybenzyl Ketone.*—Formononetin (0·35 g.) was dissolved in sodium hydroxide solution (0·4N.; 30 ml.) and heated for 15 minutes on the water-bath. After acidification, the product was filtered off (0·32 g.) and formed colourless prisms, m. p. 158°, from aqueous alcohol (Found: C, 69·8; H, 5·5. Calc. for $C_{16}H_{14}O_4$: C, 69·7; H, 5·5%). Its m. p. showed no depression on admixture with a synthetic specimen prepared by the method of Baker and Eastwood (*loc. cit.*).

This ketone (0·5 g.), acetic anhydride (5 ml.), and pyridine (2 drops) were refluxed for 15 minutes and the product (0·2 g.) was isolated and washed with water. 2 : 4-*Diacetoxyphenyl* 4′-*methoxybenzyl ketone* formed colourless prisms, m. p. 123—124°, from alcohol (Found: C, 67·2; H, 5·4. $C_{19}H_{16}O_6$ requires C, 66·7; H, 5·3%).

The hydroxy-ketone (0·2 g.) and propionic anhydride (3 ml.) were refluxed for 15 minutes and the product (0·1 g.) was isolated and washed with water. 2 : 4-*Dipropionoxyphenyl* 4′-*methoxybenzyl ketone* separated from aqueous alcohol as colourless needles, m. p. 79—80° (Found: C, 68·0; H, 6·1; OMe, 8·3. $C_{21}H_{22}O_6$ requires C, 68·1; H, 6·0; OMe, 8·4%).

2-*Hydroxy*-4-*methoxyphenyl* 4′-*Methoxybenzyl Ketone.*—This compound, prepared by the action of diazomethane on 2 : 4-dihydroxyphenyl 4′-methoxybenzyl ketone or by alkaline hydrolysis of 7 : 4′-dimethoxy*iso*flavone, crystallised from alcohol in colourless needles, m. p. 102° (Found: C, 70·4; H, 5·75; OMe, 21·7. Calc. for $C_{16}H_{14}O_4$: C, 70·6; H, 5·9; OMe, 22·8%). Wessely and Lechner (*Sitzungsber. Akad. Wiss. Wien*, 1930, **139**, 11*b*, 1061) record m. p.s 92—93° and 104°.

Isolation of Genistein.—The filtrate from the separation of formononetin was concentrated to 150 ml. and, while hot, poured into cold, stirred ether (2850 ml.). This solution was chromatographed on acid-washed alumina (500 g.), and the column eluted with alcohol–ether containing increasing amounts of alcohol. From the initial 5% alcohol–ether filtrates and the first 10% alcohol–ether eluate a pale yellow solid (28·4 g.) was obtained, and on crystallisation from aqueous alcohol this yielded formononetin (0·97 g.) and genistein (17·8 g.). From the column, cut into 5 sections each of which was extracted with 4 × 200 ml. of hot 5% hydrochloric acid in alcohol, a further quantity of genistein (6·6 g.) was obtained by evaporation to dryness, addition of water, and extraction with ether. Genistein formed

colourless needles, m. p. 300—301° (decomp.), undepressed by a synthetic sample, on crystallisation from aqueous alcohol (Found : C, 66·6; H, 3·65%; *M*, 237. Calc. for $C_{15}H_{10}O_4$: C, 66·7; H, 3·7%; *M*, 270). Light absorption in ethanol : $\varepsilon_{max.}$ 42,700 at 2625 Å. Walter (*J. Amer. Chem. Soc.*, 1941, **63**, 3273) reported a somewhat lower value for $\varepsilon_{max.}$ in 85% ethanol at the same wave-length.

Genistein (1 g.) and acetic anhydride (5 ml.), refluxed for 15 minutes and poured into water, formed triacetylgenistein (0·7 g.), colourless needles, m. p. 203—204°, from alcohol.

Prepared in a similar manner *tripropionylgenistein* formed colourless needles, m. p. 192°, from alcohol (Found : C, 66·1; H, 4·85. $C_{24}H_{22}O_8$ requires C, 65·7; H, 5·1%).

5 : 7 : 4′-*Trimethoxyisoflavone.*—(*a*) Reaction of genistein with excess of diazomethane in ether formed 5 : 7 : 4′-trimethoxy*iso*flavone, which crystallised from alcohol in colourless prisms, m. p. 162—163°, undepressed on admixture with a specimen prepared by method (*b*) (Found : C, 68·7; H, 4·9%; *M*, 296. Calc. for $C_{18}H_{16}O_5$: C, 69·2; H, 5·2%; *M*, 312).

(*b*) A solution of 2-hydroxy-4 : 6-dimethoxyphenyl 4′-methoxybenzyl ketone (Badcock, Cavill, Robertson, and Whalley, *loc. cit.*; 3·27 g.) in ethyl formate (50 ml.) was added dropwise to powdered sodium (3·2 g.) at 0°. After 24 hours at 0°, ice was added and the product extracted with ether. It crystallised from alcohol in colourless prisms, m. p. 162—163° (1·74 g.).

2-*Hydroxy*-4 : 6-*dimethoxyphenyl* 4′-*Methoxybenzyl Ketone.*—Hydrolysis of 5 : 7 : 4′-trimethoxy*iso*flavone (0·2 g.) with N-sodium hydroxide (10 ml.) and alcohol (5 ml.) for 2 hours on the water-bath formed 2-hydroxy-4 : 6-dimethoxyphenyl 4′-methoxybenzyl ketone, prisms (from benzene–light petroleum), m. p. 88—89°, undepressed by a synthetic specimen (Badcock, Cavill, Robertson, and Whalley, *loc. cit.*) (Found : C, 67·3; H, 5·95. Calc. for $C_{17}H_{18}O_5$: C, 67·5; H, 6·0%).

Œstrogenic Activity of Genistein.—The biological assays, which were carried out by Dr. D. H. Curnow, Mr. A. B. Beck, and Mr. J. D. Biggers will be reported in detail elsewhere. However, it may be stated that preliminary assays using the vaginal cornification and uterine weight methods, have shown that genistein is œstrogenically active at a total dose per mouse of 1 mg., and is probably a pro-œstrogen.

The authors thank Messrs. R. C. Rossiter and A. W. Braden for collecting the clover and supplying some " chloroplast fraction," Sir Robert Robinson for the hospitality of the Dyson Perrins Laboratory, and the British Council and the University of Western Australia for travel grants which made it possible for one of them (D. E. W.) to work for some time in Oxford.

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762. *Some 7-Substituted Derivatives of the 5α-Pregnane* Series.*

By W. KLYNE.

Some 3 : 7 : 20-substituted derivatives of pregn-5-ene and 5α-pregnane have been prepared by standard methods. The molecular optical rotations of these compounds are discussed.

THIS work was begun at a time when it was thought that the urane compounds reported by Marker, Kamm, Oakwood, Wittle, and Lawson (*J. Amer. Chem. Soc.*, 1938, **60**, 1061) might be 3 : 7-substituted derivatives of 5α-pregnane * or of an isomer of this compound. It is now known that the urane derivatives are D-homosteroids (Klyne, *Nature*, 1950, **166**, 559).

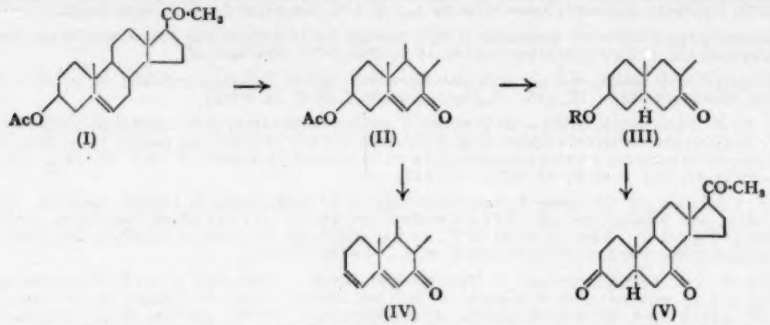
3β-Acetoxypregn-5-ene-7 : 20-dione (II), 3β-hydroxy-5α-pregnane-7 : 20-dione (III; R = H), 5α-pregnane-3 : 7 : 20-trione (V), and derivatives of these compounds have been prepared by standard methods previously used in the cholestane series.

The preparation of 5α-pregnane-3 : 7 : 20-trione completes the series of 5α-pregnanetriones most likely to be needed as reference compounds in work on naturally occurring steroids. The 3 : 6 : 20-trione has been described by Liebermann, Dobriner, Hill, Fieser, and Rhoads (*J. Biol. Chem.*, 1948, **172**, 263), the 3 : 11 : 20-trione by Steiger and Reichstein (*Helv. Chim. Acta*, 1938, **21**, 161), and the 3 : 12 : 20-trione by Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof (*J. Amer. Chem. Soc.*, 1947, **69**, 2167) and by Wagner, Moore, and Forker (*ibid.*, 1950, **72**, 1856).

The molecular rotations of the 7 : 20-diketones observed in the present work have been compared with those calculated from the rotations of previously known compounds (cf. Barton and Cox, *J.*, 1948, 783; Barton and Klyne, *Chem. and Ind.*, 1948, 755). The calculations were

* Nomenclature follows the proposals of a conference at the CIBA Foundation, London (*Chem. and Ind.*, 1951, p. SN1).

carried out on the assumption that the rotation contributions of groups in the $C_{(3)}$–C_{7} area and of a $C_{(20)}$-keto-group are independent. The results, summarized in the table, show that this



assumption is not strictly correct. A keto-group at $C_{(20)}$ does not affect the rotation changes characteristic of acetylation and oxidation at $C_{(3)}$ (Barton and Cox, *loc. cit.*). It appears,

7 : 20-*Diketones. Comparison of observed and calculated rotations.*

	$[M]_D$ observed	$[M]_D$ calc.*	Difference (obs.– calc.)
3β-Acetoxypregn-5-ene-7 : 20-dione	−274°	−238°	−36°
3β-Hydroxy-5α-pregnane-7 : 20-dione	+ 8	+ 61	−53
3β-Acetoxy-5α-pregnane-7 : 20-dione	+ 2	+ 42	−40
5α-Pregnane-3 : 7 : 20-trione	+ 71	+139	−68

* From standard values given by Barton and Klyne (*loc. cit.*).

therefore, that keto-groups at $C_{(7)}$ and $C_{(20)}$ interfere with one another's rotation contribution—*i.e.*, exert vicinal action on each other. Barton and his colleagues have shown that olefinic double bonds at $C_{(7)}$ and $C_{(22)}$ show vicinal action (Barton, Cox, and Holness, *J.*, 1949, 1771; Barton and Brooks, *J. Amer. Chem. Soc.*, 1950, **72**, 1633). Rosenkranz, Romo, Batres, and Djerassi (*J. Org. Chem.*, 1951, **16**, 298), and Djerassi, Romo, and Rosenkranz (*ibid.*, p. 754), have reported vicinal action between an olefinic double bond at $C_{(7)}$ and a keto-group at $C_{(20)}$ or the *spiro*ketal chain of the sapogenins.

Experimental.

M. p.s are corrected for emergent stem.

Specific rotations were determined in chloroform for the sodium D line, using a 0·5-dm. micro-tube; the errors are calculated as described by Klyne, Schachter, and Marrian (*Biochem. J.*, 1948, **43**, 231), except that five pairs of readings with the solution and five pairs with a solvent blank were taken in each case.

Ultra-violet absorptions were determined by using a Beckman spectrophotometer, Model DU.

Microanalyses are by Drs. Weiler and Strauss, Oxford.

The expression "usual working-up" indicates the following operations: A solution of the reaction product in an organic solvent (usually ether) was washed with N-sodium carbonate, N-sulphuric acid, and three times with water; it was then dried (Na_2SO_4) and filtered, and the solution evaporated to dryness.

Chromatography was carried out with alumina supplied by Savory and Moore, Ltd., of activity II—III according to Brockmann and Schodder (*Ber.*, 1941, **74**, 73). Other details are as given by Paterson and Klyne (*Biochem. J.*, 1948, **43**, 614). The proportions of mixed solvents are given as % (v/v).

3β-*Acetoxypregn-5-ene*-7 : 20-*dione* (II) (following Windaus, Lettré, and Schenk, *Annalen*, 1935, **520**, 98).—3β-Acetoxypregn-5-en-20-one (I) (m. p. 140—142°; 1·00 g.) was dissolved in glacial acetic acid (40 c.c.) and the solution warmed to 55° and stirred mechanically. To this, chromium trioxide (0·80 g.), dissolved in water (0·8 c.c.) and acetic acid (8 c.c.), was added dropwise during 40 minutes and the mixture was then heated for a further hour with occasional shaking, the temperature being kept at 55° throughout. The mixture was then cooled to 20°, excess of chromium trioxide reduced with aqueous sodium hydrogen sulphite, and the bulk of the acetic acid evaporated off at 100°/15 mm. The residue was cooled, then treated with water and ether, and the aqueous solution extracted five times more with ether. The ethereal solutions after the removal of all acidic material with aqueous sodium carbonate

and the usual working-up yielded 0·47 g. of yellowish solid. Two recrystallisations from aqueous ethanol gave *3β-acetoxypregn-5-ene-7 : 20-dione* as rosettes of fine shining needles, m. p. 151—153°, $[\alpha]_D^{23}$ −73·8° ± 0·8° (*c*, 1·0) (Found, on sample dried *in vacuo* at 80° : C, 74·3; H, 8·5. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·6%). The compound gave no colour with tetranitromethane in chloroform. With concentrated sulphuric acid it gave an immediate yellow colour. In the Liebermann–Burchardt reaction it gave, in the sulphuric acid layer, an immediate yellow colour, which became orange after 1 hour; the chloroform layer remained colourless. The ultra-violet absorption (kindly determined by Mr. J. Glover, University of Liverpool) showed $\lambda_{max.}$ 234·5, 390 μ (log $\varepsilon_{max.}$ 4·26, 1·85).

The *monosemicarbazone* was prepared by treating the compound (14 mg., 0·038 millimole) in methanol (1·0 ml.) with a solution of semicarbazide hydrochloride (6·7 mg., 0·06 millimole) and sodium acetate (5·2 mg., 0·06 millimole; anhyd.), in water (0·03 ml.). The mixture was left for 3 hours at room temperature and the precipitate which formed was filtered off and recrystallized from methanol (cf. androsta-3 : 5-diene-7 : 17-dione, which gave a monosemicarbazone in similar conditions; Billeter and Miescher, *Helv. Chim. Acta*, 1948, **31**, 629). The product formed microscopic prisms, m. p. 231—234° (decomp.) (Found : N, 9·8. $C_{24}H_{35}O_4N_3$ requires N, 9·8%).

3β-Hydroxy-5α-pregnane-7 : 20-dione (III; R = H).—3β-Acetoxypregn-5-ene-7 : 20-dione (300 mg.) was reduced in ethyl acetate solution with hydrogen and Adams's platinum oxide catalyst at atmospheric pressure and temperature for 30 minutes. The product, after filtration and evaporation, was dissolved in glacial acetic acid (10 c.c.) and treated with chromium trioxide (80 mg.) in acetic acid (4 c.c.) for 8 hours at room temperature, to oxidize any secondary alcoholic groups to keto-groups. After working-up as described above for the unsaturated compound, the product formed needles (240 mg.). Chromatography of this material and recrystallization of the middle fractions (eluted with light petroleum–benzene, 80 : 20 and 50 : 50) from ethyl acetate–light petroleum (b. p. 40—60°) yielded the saturated acetoxy-diketone (III; R = Ac), m. p. 169—170°. The ultra-violet absorption of this product at 233 mμ showed that it contained about 2% of the unsaturated compound (II).

The saturated compound was finally freed from unsaturated impurities by taking advantage of the fact that 5-ene-3β-hydroxy-7-keto-compounds are decomposed when heated with hydrogen chloride (Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 567) to give 3 : 5-diene-7-ketones (IV), which can be readily separated from the 3β-hydroxy-7-ketones by chromatography. Crude 3β-acetoxy-5α-pregnane-7 : 20-dione (550 mg.) in methanol (30 c.c.) was treated with potassium carbonate (500 mg.) in water (5 c.c.), and the mixture refluxed for 3 hours. It was then cooled and made acid to litmus with concentrated hydrochloric acid (1·5 c.c.). A further 5 c.c. of concentrated hydrochloric acid were added and the mixture was refluxed again for 1·5 hours. Most of the methanol was evaporated, the residue was taken up in ether and water, and the usual working-up yielded a white solid (450 mg.; m. p. 180—195°). This was chromatographed on alumina. Light petroleum–benzene mixtures eluted a small quantity of gummy solid; benzene and benzene–ether (90 : 10 and 80 : 20) eluted 283 mg. of solid, m. p. 203—210°. Benzene–ether (60 : 40 and 20 : 80) eluted about 100 mg. of material of lower m. p., which has not been further investigated. The material of m. p. 203—210°, after recrystallization from ethyl acetate (8 c.c.) and light petroleum (15 c.c.; b. p. 40—60°), gave *3β-hydroxy-5α-pregnane-7 : 20-dione* as small glistening leaflets, m. p. 209—211°, $[\alpha]_D^{23}$ +2·3° ± 0·3° (*c*, 2·2). This material showed no selective absorption between 230 and 240 mμ (Found, on sample sublimed at 150—170°/0·5 μ : C, 76·0; H, 9·7. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%).

The compound gave no colour with tetranitromethane in chloroform; it dissolved in concentrated sulphuric acid to give a colourless solution which became very pale yellow after 30 minutes. In the Liebermann–Burchardt test the chloroform layer remained colourless throughout; the sulphuric acid layer was colourless on mixing, and became very pale yellow after 20 minutes.

The *acetate* (III; R = Ac) was prepared by treating the hydroxy-diketone with acetic anhydride in pyridine at 15—20° overnight. The product crystallised from ethanol as very fine needles, m. p. 173—174°, $[\alpha]_D^{23}$ +0·5° ± 0·3° (*c*, 2·1) (Found, on sample dried *in vacuo* at 110° : C, 73·6; H, 8·9. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1%).

The *disemicarbazone* was prepared by treating the hydroxy-diketone with a large excess of semicarbazide hydrochloride and sodium acetate in aqueous methanol at room temperature for 3 days. The product was precipitated with water, filtered, dried, and recrystallized from ethanol, giving a white amorphous powder. It did not melt up to 310° (Found : N, 19·2. $C_{23}H_{38}O_2N_6$ requires N, 18·8%).

5α-Pregnane-3 : 7 : 20-trione (V).—3β-Hydroxy-5α-pregnane-7 : 20-dione (134 mg., 0·4 millimole) in glacial acetic acid (5 c.c.) was treated with chromium trioxide (47 mg., 0·47 millimole) in glacial acetic acid (3 c.c.) and set aside at 15—20° for 24 hours. Excess of chromium trioxide was then reduced by the addition of a few drops of ethanol. The usual working-up gave *5α-pregnane-3 : 7 : 20-trione*, which after two recrystallisations from ethanol formed needles, m. p. 206—208°, $[\alpha]_D^{24}$ +22·5° ± 0·4° (*c*, 2·0) (Found, on sample sublimed at 140—170°/0·5 μ : C, 75·8; H, 9·2. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·1%). In the Liebermann–Burchardt, concentrated sulphuric acid, and tetranitromethane colour reactions, the same results were obtained as with 3β-hydroxy-5α-pregnane-7 : 20-dione.

The *trisemicarbazone*, prepared as was the disemicarbazone of 3β-hydroxy-5α-pregnane-7 : 20-dione, was a white granular powder which became brown at 235—240° but did not melt up to 320° (Found : N, 24·6. $C_{24}H_{39}O_3N_9$ requires N, 25·1%).

The author is indebted to the Agricultural Research Council for a grant for expenses and to N. V. Organon, Oss, Holland, for a generous gift of pregnenolone acetate.

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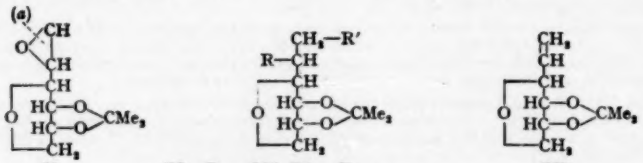
763. *Mechanism of the Reaction of Terminal Vicinal Ditoluene-p-sulphonyl Hexitol Derivatives with Sodium Iodide in Acetone.*

By A. B. Foster and W. G. Overend.

The reaction of terminal vicinal toluene-*p*-sulphonyloxy-residues in carbohydrates with sodium iodide in dry acetone to yield unsaturated products has been studied by using 1-toluene-*p*-sulphonyl and 1 : 2-ditoluene-*p*-sulphonyl derivatives of 3 : 6-anhydromannitol. A mechanism of the reaction is suggested which postulates the intermediate formation of an iodo-compound, with the iodine substituent located on the primary position, which on subsequent intramolecular transition produces the unsaturated derivative.

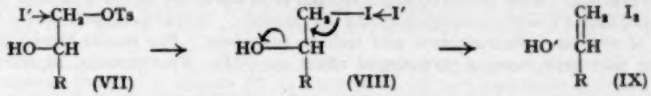
Exceptions to the rule formulated by Oldham and Rutherford, (*J. Amer. Chem. Soc.*, 1932, **54**, 366; see also Levene and Raymond, *J. Biol. Chem.*, 1933, **102**, 317) for distinguishing between primary and secondary toluene-*p*-sulphonyloxy-groups have been recorded. Thus, (*a*) the presence of an activating group adjacent to a secondary toluene-*p*-sulphonyl ester group facilitates an exchange reaction with sodium iodide in acetone; both the $-CH=CH-$ (Laland, Overend, and Stacey, *J.*, 1950, 738) and the methylene groups (Foster and Overend, unpublished observations; cf. Foster, Overend, and Stacey, *J.*, 1951, 988) are effective in this respect. (*b*) The 2 : 5-ditoluene-*p*-sulphonyl esters of 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol undergo similar exchange reactions (Wiggins and Wood, *J.*, 1951, 1180). In this case the unusual reactivity is attributed to the peculiar stereochemistry of these dianhydrohexitol derivatives, since it is found that the two sulphonyloxy-groups are replaced in the mannitol derivative whereas only one undergoes reaction in the sorbitol derivative. Moreover, this stereochemical explanation is supported by the fact that the corresponding derivative of L-iditol does not undergo any exchange reaction. (*c*) Compounds, in particular carbohydrates, which contain terminal vicinal toluene-*p*-sulphonyl ester groups [*i.e.*, $\cdot CH(OTs)\cdot CH_2\cdot OTs$] react with sodium iodide in dry acetone to yield unsaturated products (cf., also, Bell, Friedman, and Williamson, *J.*, 1937, 252, and Raymond and Schroeder, *J. Amer. Chem. Soc.*, 1948, **70**, 2786). Elimination of both the toluene-*p*-sulphonyloxy-residues occurs and no iodo-derivative can be isolated. This investigation deals with some aspects of reaction (*c*).



Suitable compounds for this study were prepared by treating 4 : 5-*iso*propylidene 1 : 2-3 : 6-dianhydromannitol (I) (Foster and Overend, *J.*, 1951, 1132) with hydriodic acid or methylmagnesium iodide, both of which yielded 4 : 5-*iso*propylidene 3 : 6-anhydro-1-deoxy-1-iodomannitol (II) by scission of the epoxide ring at (*a*). (II) readily afforded a 2-toluene-*p*-sulphonyl derivative (III). With an excess of toluene-*p*-sulphonyl chloride in dry pyridine 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (Foster and Overend *J.*, 1951, 680) gave the 1 : 2-ditoluene-*p*-sulphonyl derivative (IV) whereas the use of 1 mol. of the same reagent at 0° afforded 4 : 5-*iso*propylidene 1-toluene-*p*-sulphonyl 3 : 6-anhydromannitol (V).

The nature of the reaction of carbohydrate derivatives containing the grouping $\cdot CH(OH)\cdot CH_2\cdot OTs$ (*e.g.*, V) with sodium iodide in acetone was outlined by Friedman and Williamson (*loc. cit.*) who recorded that 1 : 2-*iso*propylidene 6-toluene-*p*-sulphonyl D-glucose could be converted into a derivative of D-glucoseen (5 : 6-didehydro-5 : 6-dideoxy-D-glucose). Similarly 6-toluene-*p*-sulphonyl 1 : 4-anhydrosorbitol afforded 1 : 4-anhydrosorbitoleen (Raymond and Schroeder, *loc. cit.*). It is probable that these reactions proceed in two stages :

(1) anionic attack at the terminal carbon atom in (VII) results in replacement of the toluene-*p*-sulphonyloxy-group by iodine to give (VIII); (2) anionic attack at the iodine atom in (VIII)



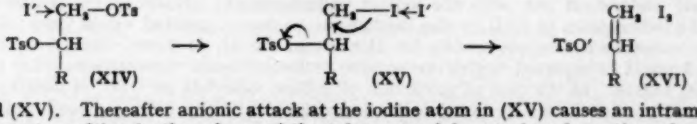
(VII) (VIII) (IX)

results in an intramolecular displacement with the ejection of a hydroxyl ion, formation of molecular iodine, and the establishment of an ethylenic linkage (IX). In support of this view it was shown that treatment of 4 : 5-*iso*propylidene 1-toluene-*p*-sulphonyl 3 : 6-anhydromannitol (V) with sodium iodide (1·2 mols.) in dry acetone at 80—90° for 3 hours resulted in 91·2% replacement of the toluene-*p*-sulphonyloxy-residue by iodine, and 4 : 5-*iso*propylidene 3 : 6-anhydro-1-deoxy-1-iodomannitol (II) was obtained [cf. (VII) ⟶ (VIII)]. (II) on treatment with sodium iodide (1·2 mols.) in dry acetone at 140—145° for 12 hours did not undergo any further reaction, but, by increasing the molar proportion of sodium iodide (to 8·8 mols.) and heating at 210—220° for 12 hours, iodine was liberated and 4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen (VI) was formed [cf. (VIII) ⟶ (IX)]. Thus the conversion (VII) ⟶ (IX) may be readily differentiated into two stages of which the first stage may be effected with greater ease.

The reactions of derivatives containing the grouping ·CH(OTs)·CH_2·OTs with sodium iodide in acetone differ from those described above since they proceed more readily and it is not possible to isolate intermediate compounds. The first example of this type of reaction was encountered by Levene and Mehltretter (*Enzymologia*, 1937, **4**, 232) who found that all the toluene-*p*-sulphonyloxy-groups in 1 : 2 : 3-tritoluene-*p*-sulphonyl D-glycerol were eliminated and an unsaturated product resulted (see also Tipson and Cretcher, *J. Org. Chem.*, 1943, **8**, 95; Hann, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73; Karrer, Schick, and Schwyzer, *Helv. Chim. Acta*, 1948, **31**, 784; Karrer and Davis, *ibid.*, p. 1611; Owen and Bladon, *J.*,

$$\underset{(X)}{R{\cdot}CH(OTs){\cdot}CH_2{\cdot}OTs} \longrightarrow \underset{(XI)}{R{\cdot}CH(OTs){\cdot}CH_2I} \longrightarrow \underset{(XII)}{R{\cdot}CHI{\cdot}CH_2I} \longrightarrow \underset{(XIII)}{R{\cdot}CH{:}CH_2}$$

1950, 598; Foster and Overend, *loc. cit.*). It was suggested by Owen and Bladon (*loc. cit.*) that the reaction proceeded in three stages, (X) ⟶ (XIII), and that it would not be possible to isolate the intermediate (XII). The second suggestion was based on previous work by Finkelstein (*Ber.*, 1910, **43**, 1528) and by Büllman (*Rec. Trav. chim.*, 1916, **36**, 313; 1917, **37**, 245) who showed that vicinal di-iodo-compounds could not be prepared by the action of sodium iodide in acetone on the corresponding dibromo- or dichloro-derivatives, unsaturated products being invariably obtained. An alternative mechanism, however, may account for the results: Anionic attack at the primary carbon atom in (XIV) may result in a normal iodine exchange,



(XIV) (XV) (XVI)

to afford (XV). Thereafter anionic attack at the iodine atom in (XV) causes an intramolecular displacement resulting in the release of the toluene-*p*-sulphonate ion, formation of molecular iodine, and establishment of an ethylenic linkage (XVI) [cf. (VII) ⟶ (VIII) ⟶ (IX)]. The action of sodium iodide, sodium trifluoroacetate, and sodium salicylate in acetone on 4 : 5-*iso*propylidene 1 : 2-ditoluene-*p*-sulphonyl 3 : 6-anhydromannitol (IV) and 4 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxy-1-iodomannitol (III) provided evidence in support of this. The product in each case with sodium iodide was 4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen (VI). The results summarized in Table I show that the conversion (III) ⟶ (VI) [in the general case (XV) ⟶ (XVI)] proceeds at room temperature, whereas under similar conditions (IV) [in the general case (XIV)] is unaffected.

These results explain our previous failure to obtain (III) by treatment of (IV) with sodium iodide in acetone under very mild conditions (Foster and Overend, *loc. cit.*), since the conditions necessary to effect the conversion (IV) ⟶ (III) are those under which (III) when formed would be converted rapidly into (VI). Hence, in derivatives of the type R·CH(OTs)·CH_2·OTs the second stage of their reaction with sodium iodide in acetone is the readier whereas in derivatives of the type R·CH(OH)·CH_2·OTs the first stage is the readier.

It follows that if the mechanism suggested above, (XIV) ⟶ (XVI), is valid, then it should be possible to effect the second stage, (XV) ⟶ (XVI), by the anion of any sodium salt which is soluble in acetone. Most of the common sodium salts are either of low solubility or insoluble in acetone and hence a wide investigation was not possible. It was feasible however to examine the action of sodium trifluoroacetate and sodium salicylate. The results shown in Table II demonstrate that both have a pronounced effect on (III). Furthermore, in reactions on a larger scale it was possible to isolate the well-anthenticated **4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen** in each case. These salts had no effect on the 1 : 2-ditoluene-*p*-sulphonyl derivative (IV), suggesting that their reaction with (III) is by anionic attack at the iodine atom [cf. (XV)]. Moreover, it may be seen from Table II that the discrepancies between the values determined by the methods A and B are 28% and 55·2% respectively for the scdium trifluoroacetate and the sodium salicylate, whereas in Table I for sodium iodide they do not exceed 5% which is near the limit of experimental error. The reasons for these discrepancies are not completely understood but, with the sodium trifluoroacetate, attack by the trifluoroacetate ion on the iodine atom in (III) by the mechanism we have suggested would yield $CF_3{\cdot}CO{\cdot}OI$ which is known to decompose readily (cf. Henne and Zinner, *J. Amer. Chem. Soc.*, 1951, **73**, 1362) and would be expected to give rise to some molecular iodine together with other products containing iodine. In the case of the action of sodium salicylate on (III), in addition to the unsaturated product **4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen** (VI), a second, unidentified substance was obtained, having m. p. 68—69°, which did not contain iodine or sulphur or an ethylenic linkage and was optically inactive; this compound may be one of the breakdown products of $HO{\cdot}C_6H_4{\cdot}CO{\cdot}OI$.

TABLE I.

Extent (%) *of exchange reaction on treatment of* (III) *and* (IV) *with sodium iodide in acetone* (see Experimental).

Compound	Reaction conditions: 15—20° 30 hrs.	130—135° 1 hr.	100—105° 5 hrs.	130—135° 6 hrs.	Method of determination *
4 : 5-*iso*Propylidene 1 : 2-ditoluene-*p*-sulphonyl 3 : 6-anhydromannitol (IV)	—	32·6	45·8	64·0	A
	—	36·5	50·7	68·4	B
4 : 5-*iso*Propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxy-1-iodomannitol (III)	38·6	48·2	59·2	—	A
	37·8	52·6	60·1	—	B

* A, % exchange determined from the wt. of sodium toluene-*p*-sulphonate pptd. B, % exchange determined by titration of the liberated iodine.

TABLE II

Action of sodium trifluoroacetate and sodium salicylate in acetone on (III). *Extent* (%) *of exchange reaction.*

Mannitol derivative	Reactions conditions: $CF_3{\cdot}CO_2Na$, 120—130° for 3 hours	o-$HO{\cdot}C_6H_4{\cdot}CO_2Na$, 120—130° for 5 hours	Method of determination *
4 : 5-*iso*Propylidene 1-iodo-	43·4	77·1	A
2-Toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxy-	15·4	21·9	B

* A and B as in Table I.

From our results it seems that the mechanism of the reaction of terminal vicinal ditoluene-*p*-sulphonyl derivatives with sodium iodide in dry acetone is not completely explained by the three-stage reaction [(X) ⟶ (XIII)] suggested by Owen and Bladon (*loc. cit.*) which involves a vicinal di-iodo-intermediate derivative. It appears that the alternative mechanism now suggested, *i.e.*, (XIV) ⟶ (XVI), offers a more satisfactory explanation of the conversion of **4 : 5-*iso*propylidene 1 : 2-ditoluene-*p*-sulphonyl 3 : 6-anhydromannitol** (IV) into **4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen** (VI) by the action of sodium iodide in acetone.

EXPERIMENTAL.

Action of Methylmagnesium Iodide on **4 : 5-iso*Propylidene* 1 : 2-3 : 6-*Dianhydromannitol*.**—To a boiling ethereal solution of methylmagnesium iodide [prepared from magnesium (0·3 g.), methyl iodide (0·75 c.c.) and dry ether (5 c.c.)], a solution of **4 : 5-*iso*propylidene 1 : 2-3 : 6-dianhydromannitol** (1·0 g.) in dry ether (10 c.c.) was added gradually during 30 minutes. After a further 3 hours the ethereal

solution was poured into ice-cold dilute sulphuric acid, and the aqueous layer extracted with chloroform (3 × 30 c.c.). The combined extracts were washed with dilute aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The syrupy residue gradually crystallized and recrystallization from light petroleum (b. p. 40—60°) gave **4 : 5-iso*propylidene* 3 : 6-*anhydro*-1-*deoxy*-1-*iodomannitol*** (1·2 g.) as colourless prisms, m. p. 75—76°, $[\alpha]_D^{20}$ −44·6° (*c*, 0·99 in chloroform) (Found: C, 34·2; H, 4·9; I, 40·6. $C_9H_{15}O_4I$ requires C, 34·4; H, 4·8; I, 40·4%).

Action of Hydriodic Acid on **4 : 5-iso*Propylidene* 1 : 2-3 : 6-*Dianhydromannitol***.—A solution of dianhydro-compound (2·49 g.) in acetone (87 c.c.) and water (37 c.c.) containing hydriodic acid (0·35 c.c.; 43%) was boiled under reflux for 1·5 hours. Thereafter the solution was neutralised with lead carbonate, and the insoluble residues collected and well washed with acetone. The filtrate was evaporated to small bulk and extracted with ether (3 times; total volume, 100 c.c.). The combined extracts after being dried ($MgSO_4$) were evaporated to 20 c.c. Coloured impurities were removed by shaking with charcoal. Evaporation to dryness gave a colourless syrup which after dissolution in ether–light petroleum (b. p. 60—80°) yielded large colourless prisms (2·6 g.), m. p. 75—76°, $[\alpha]_D^{20}$ −43·2° (*c*, 1·62 in chloroform). These were **4 : 5-*iso*propylidene 3 : 6-anhydro-1-deoxy-1-iodomannitol** (mixed m. p.).

4 : 5-iso*Propylidene* 2-*Toluene*-p-*sulphonyl* 3 : 6-*Anhydro*-1-*deoxy*-1-*iodomannitol*.—**4 : 5-*iso*Propylidene 3 : 6-anhydro-1-deoxy-1-iodomannitol** (6·42 g.) in dry pyridine (26 c.c.) was treated at room temperature for 3 days with toluene-*p*-sulphonyl chloride (6·5 g., 1·65 mols.). On dilution of the mixture with water an oily product separated which gradually solidified. This was collected and dissolved in chloroform. The solution was washed successively with ice-cold dilute hydrochloric acid and dilute aqueous sodium hydrogen carbonate and dried ($MgSO_4$). On evaporation a residue was obtained which after recrystallization from aqueous methanol afforded **4 : 5-iso*propylidene* 2-*toluene*-p-*sulphonyl* 3 : 6-*anhydro*-1-*deoxy*-1-*iodomannitol*** (5·25 g.) as colourless prisms, m. p. 90—91°, $[\alpha]_D^{20}$ −65·4° (*c*, 1·7 in chloroform) (Found: C, 41·6; H, 4·5; S, 7·2. $C_{16}H_{21}O_6SI$ requires C, 41·0; H, 4·5; S, 6·8%).

4 : 5-iso*Propylidene* 1 : 2-*Ditoluene*-p-*sulphonyl* 3 : 6-*Anhydromannitol*.—This substance, prepared according to the method of Foster and Overend (*loc. cit.*), had m. p. 125—126° and $[\alpha]_D^{20}$ −31·7° in chloroform.

4 : 5-iso*Propylidene* 1-*Toluene*-p-*sulphonyl* 3 : 6-*Anhydromannitol*.—**4 : 5-*iso*Propylidene 3 : 6-anhydromannitol** (1·0 g.) (Foster and Overend, *loc. cit.*) in dry pyridine (10 c.c.) at 0° was treated with toluene-*p*-sulphonyl chloride (0·94 g., 0·98 mol.) gradually during 2 hours. Thereafter the mixture was set aside at room temperature for 24 hours and then poured into water (250 c.c.). The crystalline product which separated was collected and well washed with water. Recrystallization from aqueous methanol afforded the **1-*toluene*-p-*sulphonyl*** derivative (0·95 g.) as colourless needles, m. p. 133—134°, $[\alpha]_D^{20}$ −21·8° (*c*, 1·2 in chloroform) (Found: C, 53·9; H, 6·2. $C_{16}H_{22}O_7S$ requires C, 53·6; H, 6·1%).

Stability of **4 : 5-iso*Propylidene* 2-*Toluene*-p-*sulphonyl* 3 : 6-*Anhydro*-1-*deoxy*-1-*iodomannitol***.—The toluene-*p*-sulphonyl derivative (100 mg.) in dry acetone (5 c.c.) was heated at 130—135° for 4 hours. The solution remained colourless throughout this period. Evaporation of the acetone solution gave unchanged starting material (80 mg.), m. p. 89—90°.

Action of Sodium Iodide in Acetone on the Foregoing Toluene-p-sulphonyl Derivatives.—(a) **4 : 5-iso*Propylidene ditoluene*-p-*sulphonyl* 3 : 6-*anhydromannitol***. A solution of the ditoluene-*p*-sulphonyl derivative (3·0 g.) and sodium iodide (3·0 g.) in dry acetone (25 c.c.) was heated for 3 hours at 110—115°. The sodium toluene-*p*-sulphonate precipitated (2·13 g.) corresponded to 91·8% of the theoretical for the exchange of two toluene-*p*-sulphonyloxy-residues. The filtrate after removal of the sodium salt was diluted with chloroform (75 c.c.), freed from iodine by washing with dilute sodium thiosulphate solution, dried ($MgSO_4$), and evaporated. Distillation of the residue gave **4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen** (0·7 g.) as a colourless liquid, b. p. 65—75° (bath-temp.)/0·05 mm., $[\alpha]_D^{17}$ +87·5° (*c*, 1·0 in methanol) (cf. Foster and Overend, *loc. cit.*).

(b) **4 : 5-iso*Propylidene* 2-*toluene*-p-*sulphonyl* 3 : 6-*anhydro*-1-*deoxy*-1-*iodomannitol***. The mono-toluene-*p*-sulphonyl derivative (1·5 g.) in dry acetone (10 c.c.) containing sodium iodide (1·0 g., 2 mols.) was heated at 115—120° for 4 hours. The sodium toluene-*p*-sulphonate precipitated (0·591 g.) corresponded to 95·1% of that expected for the complete exchange of the toluene-*p*-sulphonyloxy-group. The filtrate, treated as above, gave **4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen** (0·45 g.), b. p. 65—70° (bath-temp.)/0·05 mm., n^{16} 1·5166, $[\alpha]_D^{20}$ +84° (*c*, 1·2 in chloroform).

(c) **4 : 5-iso*Propylidene* 1-*toluene*-p-*sulphonyl* 3 : 6-*anhydromannitol***. A solution of the toluene-*p*-sulphonyl derivative (0·72 g.) in dry acetone (10 c.c.), containing sodium iodide (0·36 g., 1·2 mols.) was heated at 80—90° for 4 hours. The sodium toluene-*p*-sulphonate precipitated (0·353 g.) corresponded to 91·2% of that expected for the complete exchange of the toluene-*p*-sulphonyloxy-residue. The filtrate after removal of the sodium salt was evaporated to dryness and extracted with boiling light petroleum (b. p. 60—80°) whence crystals of **4 : 5-*iso*propylidene 3 : 6-anhydro-1-deoxy-1-iodomannitol** (0·52 g.) separated, having m. p. 75—76° alone or on admixture with the anthentic material described above.

(d) **4 : 5-iso*Propylidene* 3 : 6-*anhydro*-1-*deoxy*-1-*iodomannitol***. The iodo-derivative (2·0 g.) in dry acetone (15 c.c.) containing sodium iodide (9 mols., 8·6 g.) was heated at 210—215° for 12 hours. The solution was then diluted with chloroform (50 c.c.) and freed from iodine by washing with dilute aqueous sodium thiosulphate, dried ($MgSO_4$), and evaporated. Distillation of the residue gave **4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen** (0·54 g.), b. p. 75—80° (bath-temp.)/0·05 mm., n^{19} 1·5160, $[\alpha]_D^{20}$ +80·2° (*c*, 1·51 in chloroform).

Comparative Iodine Exchange Experiments.—In the comparative experiments (Tables I and II), **4 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxy-1-iodomannitol** and **4 : 5-*iso*propylidene 1 : 2-ditoluene-*p*-sulphonyl 3 : 6-anhydromannitol** were used in equimolecular quantities (100 and 110 mg. respectively). The volume of acetone was constant (5 c.c.) and the molar proportions of the

various salts were as follows: sodium iodide 1·1 (35 mg.) and 2·2 mols. (70 mg.) respectively; sodium trifluoroacetate 1·1 (32 mg.) and 2·2 mols. (64 mg.) respectively; sodium salicylate 1·1 (38 mg.) and 2·2 mols. (76 mg.) respectively.

In estimating the extent of the exchange reaction the precipitated sodium toluene-*p*-sulphonate was collected in a small sintered-glass funnel, washed with dry acetone, and dried at 100—110° for 30 minutes before being weighed. The corresponding filtrate was diluted with water and the free iodine titrated with 0·05N-sodium thiosulphate.

Action of Sodium Trifluoroacetate in Acetone on 4 : 5-iso*Propylidene* 2-*Toluene*-p-*sulphonyl* 3 : 6-*Anhydro*-1-*deoxy*-1-*iodomannitol*.—The toluene-*p*-sulphonyl derivative (1·5 g.) in dry acetone (15 c.c.) containing sodium trifluoroacetate (1·5 mols., 0·72 g.) was heated at 130—135° (aluminium block) for 6 hours. The precipitated sodium toluene-*p*-sulphonate (0·60 g.), collected in the usual manner, corresponded to 96·5% of that expected for the complete release of the toluene-*p*-sulphonyloxy-residue. Titration of the filtrate with 0·05N-sodium thiosulphate (27 c.c.) indicated that 39·7% of the iodine was present in the form of free iodine. Thereafter the mixture was diluted with water (40 c.c.) and extracted with chloroform (3 × 50 c.c.). The combined extracts were dried ($MgSO_4$) and evaporated and the residue was distilled. 4 : 5-*iso*Propylidene 3 : 6-anhydromannitoleen (0·26 g.) was obtained, having b. p. 70—75° (bath-temp.)/0·05 mm., n^{19} 1·5165, $[\alpha]_D^{20}$ +82·3° (*c*, 1·1 in chloroform).

Action of Sodium Salicylate in Acetone on 4 : 5-iso*Propylidene* 2-*Toluene*-p-*sulphonyl* 3 : 6-*Anhydro*-1-*deoxy*-1-*iodomannitol*.—A solution of the toluene-*p*-sulphonyl derivative (1·5 g.) in dry acetone (15 c.c.) containing sodium salicylate (1·5 mols.; 0·76 g.) was heated at 130—135° (aluminium block) for 6 hours. Sodium toluene-*p*-sulphonate (0·57 g.), corresponding to 91·7% of that expected for the complete release of the toluene-*p*-sulphonyloxy-residue, was collected in the usual way. Titration of the filtrate with 0·05N-sodium thiosulphate (30·7 c.c.) indicated that 47·9% of the iodine was present as free iodine. The iodine-free filtrate was diluted with water and extracted with chloroform (3 × 50 c.c.), and the combined extracts were dried ($MgSO_4$) and evaporated to dryness. The straw-coloured syrup thereby obtained partly crystallized. The crystals were collected (0·18 g.) and after recrystallization from aqueous methanol were obtained as colourless feathery needles, m. p. 68—69°, $[\alpha]_D^{20}$ ±0·0° (*c*, 1·0 in chloroform) and did not contain sulphur, iodine, or an ethylenic linkage (Found: C, 62·3; H, 5·1%). This substance is so far unidentified. The residual syrup on distillation yielded 4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen (0·24 g.), b. p. 70—75° (bath-temp.)/0·05 mm., n^{19} 1·5158, $[\alpha]_D^{20}$ +84·6° (*c*, 1·5 in chloroform).

The authors thank Professor M. Stacey, F.R.S., for his interest in this work and one of them (A. B. F.) acknowledges financial assistance from the Brewing Industry Research Foundation. The expenses of the investigation were covered by a grant from Imperial Chemical Industries Limited.

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[*Received, September 4th*, 1951.]

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764. *The Reaction of Ethyl Diazoacetate with Anthracene, 1 : 2-Benzanthracene, and Pyrene.*

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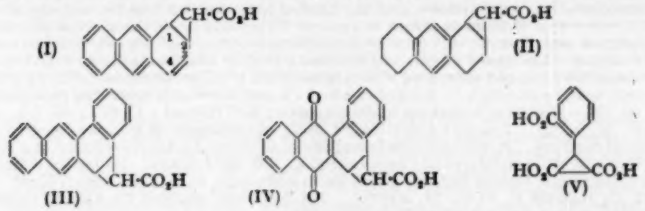
Ethyl diazoacetate reacted with anthracene, 1 : 2-benzanthracene, and pyrene to give the *cyclo*propane derivatives (I), (III), and (VI), respectively. In the case of pyrene a second, unidentified, product was also formed in small yield. The relationship of these addition reactions to osmium tetroxide addition is noted.

THE evidence for the double-bond character of certain of the bonds in aromatic compounds has recently been reviewed by one of us (Badger, *Quart. Reviews*, 1951, **5**, 147), who pointed out that there are three reagents which are especially suitable for uncovering this type of chemical reactivity. These are ozone, osmium tetroxide, and an aliphatic diazo-compound, all of which undergo addition to adjacent unsaturated carbon atoms in a molecule. Other double-bond reagents, namely halogens, and hydrogen in the presence of a catalyst, are less suitable for studying the additive reactivity of aromatic compounds—halogens because they are also substituting agents, and hydrogen because the primary addition product is prone to undergo rearrangement in the presence of a catalyst. There is also the complication that these latter reagents are able to undergo 1 : 4-addition as well as 1 : 2-addition, whereas the three reagents first mentioned show only 1 : 2-addition.

In this laboratory use has been made of osmium tetroxide to reveal the reactive bonds in fused-ring aromatic hydrocarbons, and also to compare the relative degrees of reactivity of such bonds in a series of compounds (for references, see Badger, *loc. cit.*). We have now sought to

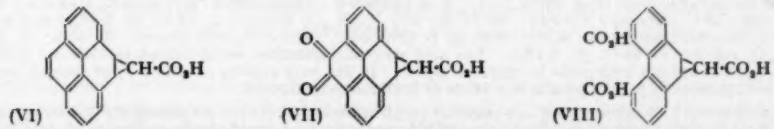
supplement this evidence by examining the reactions of some of these hydrocarbons with ethyl diazoacetate. This reagent reacts with the 1 : 2-bond of naphthalene to give ethyl 1 : 2-dihydronaphth-1 : 2-yleneacetate (Buchner and Hediger, *Ber.*, 1903, **36**, 3502) and with the 9 : 10-bond of phenanthrene to give ethyl 9 : 10-dihydrophenanthr-9 : 10-yleneacetate (Drake and Sweeney, *J. Org. Chem.*, 1946, **11**, 67; cf. Cook, Dickson, and Loudon, *J.*, 1947, 746). In a preliminary publication (*Chem. Abs.*, 1947, **41**, 6553) Clar showed that ethyl diazoacetate reacts also with anthracene, and we have extended this work and have examined in addition the behaviour of 1 : 2-benzanthracene and pyrene. The products in all three cases appeared to be derivatives of *cyclo*propanecarboxylic acid, and like the corresponding compounds from naphthalene and phenanthrene, these were stable under conditions which led to rearrangement to *cyclo*heptatriene derivatives in the case of the norcaradiene derivatives which are formed from benzene and its homologues by interaction with ethyl diazoacetate.

On account of the large amounts of unreacted hydrocarbon, the reaction products in all cases were hydrolysed with alcoholic alkali so as to facilitate separation. From anthracene there was then obtained a 10% yield of a stable acid, which is regarded as 1 : 2-dihydroanthr-1 : 2-yleneacetic acid (I), although this structure has not been fully established. The ultra-violet absorption spectrum (future communication) is quite different from that of anthracene, which



excludes the possibility that the compound is an anthrylacetic acid. The stability of the methyl ester towards osmium tetroxide and towards perbenzoic acid showed that the compound was not a *cyclo*heptatriene derivative. The acid slowly absorbed bromine to give a dibromide, which readily lost hydrogen bromide to give a monobromo acid. The acid (I) absorbed six atoms of hydrogen. These properties are all consistent with the structure (I), and the hydrogenated compound is regarded as the octahydroanthracene derivative (II); its absorption spectrum supports this view. The 1 : 2-positions are assigned to the *cyclo*propane ring largely by analogy with the compound from naphthalene, and because osmium tetroxide attacks anthracene at these positions (Cook and Schoental, *Nature*, 1948, **161**, 237). With osmium tetroxide, however, the 3 : 4-bond is also attacked so that a tetrol results. The relative stability of the 3 : 4-bond in (I) is to be ascribed to the fact that this bond participates, together with the 1 : 2-*cyclo*propane ring, in a closed conjugated system. That a *cyclo*propane ring can conjugate with other unsaturated centres is well recognised.

1 : 2-Benzanthracene likewise reacted with ethyl diazoacetate, and, after hydrolysis, there was obtained a 7% yield of 3 : 4-dihydro-1 : 2-benzanthr-3 : 4-yleneacetic acid (III), which absorbed one molecule of hydrogen on microhydrogenation with palladium charcoal, probably at the 9 : 10-positions. Oxidation with sodium dichromate in acetic acid gave the quinone-acid (IV), the structure of which followed from its further oxidation with alkaline hydrogen peroxide to the known 3-*o*-carboxyphenyl*cyclo*propane-1 : 2-dicarboxylic acid (V). Addition to the 3 : 4-positions of 1 : 2-benzanthracene is in harmony with the reaction of this hydrocarbon with osmium tetroxide (Cook and Schoental, *J.*, 1948, 170).



From the reaction of pyrene with ethyl diazoacetate there was isolated in 5% yield the colourless 1 : 2-dihydropyren-1 : 2-yleneacetic acid (VI) and also a 0·5% yield of a yellow acid which appeared to be isomeric with this. Both the yellow acid and its methyl ester were exceedingly sparingly soluble and inert, and we have obtained no evidence as to their structure. The

major product of this reaction, which on microhydrogenation absorbed one molecule of hydrogen, was clearly (VI) as it was oxidised by chromic acid to a red acid with the properties of an *o*-quinone. This was evidently (VII), although it could not be obtained analytically pure. Further oxidation with alkaline hydrogen peroxide led to the tricarboxylic acid (VIII), isolated as its trimethyl ester. Thus, although pyrene gave an inhomogeneous product with ethyl diazoacetate, addition took place mainly at the 1 : 2-positions, which are also the positions attacked by osmium tetroxide and by ozone.

It should be emphasised that in all three cases under consideration the positions attacked by the " double-bond reagents " are different from those attacked by reagents which effect electrophilic substitution.

Experimental.

1 : 2-*Dihydroanthr*-1 : 2-*yleneacetic Acid* (I).—Ethyl diazoacetate (9·5 g.) was added during 4 hours to a stirred solution of pure anthracene (59 g.) in decalin (300 c.c.) at 140—145°. [The decalin had been purified by repeated shaking with concentrated sulphuric acid until a sample decolorised bromine water only on long storage.] Then the temperature was raised to 160° during an hour and maintained there for a further hour. The cooled solution was filtered, and most of the decalin removed in steam. The residue was recombined with the filtered solid and boiled under reflux for 3 hours with 10% alcoholic sodium hydroxide (500 c.c.). About 350 c.c. of the alcohol were distilled and the suspension remaining was diluted with water and distilled in steam to remove the remainder of the alcohol and the decalin. The boiling suspension was filtered; the recovered anthracene (54—55 g.) was suitable for retreatment with ethyl diazoacetate. The cooled filtrate was acidified and after 2 hours the sticky solid was collected, washed with benzene (20 c.c.), and triturated with ethanol (5 c.c.). The residual solid (2·2 g.) was recrystallised from acetic acid, from which 1 : 2-*dihydroanthr*-1 : 2-*yleneacetic acid* separated as a white crystalline powder, m. p. 282—284° after beginning to decompose at 240° (Found : C, 81·1; H, 5·3. $C_{18}H_{12}O_2$ requires C, 81·8; H, 5·1%). The acid absorbed 3·1 mols. of hydrogen on microhydrogenation over a palladium–charcoal catalyst. It was recovered completely unchanged after its solution in a large excess of sodium hydroxide in ethylene glycol had been heated at 160° for 5 hours. Its *methyl* ester, prepared with ethereal diazomethane, formed lustrous plates (from methanol), m. p. 123—124° (Found : C, 81·55; H, 5·75. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·65%). The acid was oxidised by sodium dichromate in acetic acid, but a homogeneous product could not be isolated.

s-*Octahydroanthr*-1 : 2-*yleneacetic Acid* (II).—A solution of methyl dihydroanthryleneacetate (0·27 g.) in acetic acid (10 c.c.) was shaken with hydrogen and Adams's platinum catalyst (0·09 g.). When the slow absorption had ceased the solution was concentrated under reduced pressure and treated with water. The precipitated gum was treated with ethereal diazomethane to re-esterify any acid formed by hydrolysis. The *methyl* ester of (II) then formed soft polyhedra (from methanol), m. p. 79—80° (Found : C, 79·8; H, 7·7. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·9%). The *acid*, formed by hydrolysis, crystallised from petroleum (b. p. 100—120°) in lustrous plates, m. p. 192—193° (Found : C, 79·6; H, 7·5. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%).

Bromination of 1 : 2-*Dihydroanthr*-1 : 2-*yleneacetic Acid*.—(*a*) A solution of the methyl ester in carbon disulphide was treated with bromine (1·1 mol.) in carbon disulphide and kept for ½ hour, by which time the solution was almost colourless. The ester dibromide remaining on evaporation formed a yellow powder (from methanol) which decomposed at 145° (Found : C, 54·7; H, 4·3. $C_{17}H_{14}O_2Br_2$ requires C, 49·8; H, 3·45%). These figures show that considerable loss of hydrogen bromide from the dibromide had taken place.

(*b*) The acid (0·1 g.) was treated with bromine (1·1 mol.) in acetic acid. After ½ hour the solution was boiled for 15 minutes, hydrogen bromide being evolved. The solution was concentrated under reduced pressure, and the product precipitated with water. Treatment of the acid with ethereal diazomethane gave *methyl* 3-(or 4-)*bromo*-1 : 2-*dihydroanthr*-1 : 2-*yleneacetate*, which crystallised from light petroleum in needles, m. p. 202—204° (Found : C, 62·2; H, 4·1. $C_{17}H_{13}O_2Br$ requires C, 62·0; H, 4·0%).

3 : 4-*Dihydro*-1 : 2-*benzanthr*-3 : 4-*yleneacetic Acid* (III).—Pure 1 : 2-benzanthracene (26 g.) in purified decalin (40 c.c.) was treated with ethyl diazoacetate (4 g.) as described for anthracene. After hydrolysis of the product with alcoholic sodium hydroxide and removal of residual solvents, the crude, brown acidic product was dissolved in acetic acid (8 c.c.), and the solution kept for 10 days, the walls of the flask being scratched occasionally. The material which separated (0·8 g.) was obtained pure by several recrystallisations from acetic acid. 3 : 4-*Dihydro*-1 : 2-*benzanthr*-3 : 4-*yleneacetic acid* (III) had m. p. 290—291° (decomp.) (Found : 83·7; H, 5·1. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·9%), and with ethereal diazomethane gave a *methyl* ester, m. p. 149—150° (from methanol) (Found : C, 83·9; H, 5·4. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·4%). The acid was not isomerised when heated for 5 hours with a large excess of sodium hydroxide in ethylene glycol. It was only slightly attacked by prolonged treatment with potassium permanganate in acetone or bromine in acetic acid.

3 : 4-*Dihydro*-1 : 2-*benzanthra*-9 : 10-*quinon*-3 : 4-*yleneacetic Acid* (IV).—A solution of sodium dichromate (1·6 g.) in 80% acetic acid (10 c.c.) was added gradually to a gently boiling solution of acid (III) (0·4 g.) in acetic acid (20 c.c.), and boiling was continued for ½ hour. The solution was concentrated under reduced pressure and then diluted with water, and the yellow flocculent precipitate collected. This was best freed from tarry by-products by crystallisation from benzene, from which the *quinone-acid* (IV) separated as orange micropolyhedra, m. p. 278—280° (decomp.) (Found : C, 76·1; H, 3·9. $C_{20}H_{12}O_4$ requires C, 75·9; H, 3·8%). Zinc dust and dilute ammonia solution gave an intense red colour.

For further oxidation, a warm solution of this quinone-acid (100 mg.) in water (5 c.c.) and sodium hydroxide (70 mg.) was treated with dilute hydrogen peroxide, added in portions during the course of an hour or so, until the solution was almost colourless. It was boiled for 10 minutes, acidified with dilute sulphuric acid, saturated with salt, and extracted with ether and ethyl acetate. The combined extracts were evaporated and the residue was sublimed at 5 mm. into two fractions, (i) below 240°, and (ii) 240—280°. Fraction (ii) was resublimed, giving a colourless powder, m. p. 272—274°. The mixed m. p. with an authentic sample of 3-*o*-carboxyphenyl*cyclo*propane-1 : 2-dicarboxylic acid (V) (cf. Drake and Sweeney, *loc. cit.*) was 274—276°.

1 : 2-*Dihydropyren*-1 : 2-*yleneacetic Acid* (VI).—Pure pyrene (40 g.) in decalin (40 c.c.) was treated with ethyl diazoacetate (7·5 g.), and the products were worked up as described for the analogous reaction with anthracene. The recovered pyrene, suitable for retreatment, amounted to about 37 g. The crude acidic product was boiled under reflux for 20 minutes with ether (150 c.c.) and then filtered. The filtrate was evaporated and the residue triturated at 0° with ethanol (5—10 c.c.). The resulting yellow powder (0·7 g.) gave, on crystallisation from acetic acid, colourless needles, m. p. 267—268°, of 1 : 2-*dihydropyren*-1 : 2-*yleneacetic acid* (Found : C, 83·3; H, 4·9. $C_{18}H_{12}O_2$ requires C, 83·1; H, 4·65%), which formed a *methyl* ester, m. p. 142—143° (from methanol) (Found : C, 83·2; H, 5·2. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·2%). The acid was unchanged after being heated for 5 hours with sodium hydroxide in ethylene glycol.

The residue from the ether extraction of the crude acidic product was exceedingly sparingly soluble in all solvents. The material from four experiments as described above was suspended in excess of ethereal diazomethane and kept overnight; this treatment was repeated. The ether was removed and the residue dissolved in boiling toluene (300 c.c.). The cooled solution was passed through a column of alumina. Evaporation of the eluate and crystallisation from toluene gave fine, intensely yellow needles (150 mg.), m. p. 280—282° (Found : C, 83·45; H, 4·73%). On prolonged boiling with excess of alcoholic sodium hydroxide this *ester* was hydrolysed to a yellow acid which decomposed above 340°. It was insoluble, except in boiling nitrobenzene.

Oxidation of 1 : 2-*Dihydropyren*-1 : 2-*yleneacetic Acid* (VI).—A solution of chromic acid (1·6 g.) in 80% acetic acid (5 c.c.) was added during an hour to a gently boiling solution of the acid (VI) (0·4 g.) in acetic acid (15 c.c.). Boiling was continued for ½ hour, and the solution was concentrated, diluted with water, and kept overnight. The deep red microscopic needles (95 mg.) were collected. This acid, m. p. 300—320° (decomp.), was evidently (VII) but it could not be obtained free from chromium, even by recrystallisation from toluene. *o*-Phenylenediamine gave a neutral yellow amorphous product; the carboxyl group had evidently reacted as well as the *o*-quinonoid group. Attempts to prepare a methyl ester were also fruitless, owing to reactivity of the quinone group. An alkaline solution became pale yellow when saturated with sulphur dioxide, the red quinone being reprecipitated after boiling with dilute acid.

For further oxidation, this quinone-acid (50 mg.) was dissolved in dilute sodium carbonate solution (5 c.c.), and hydrogen peroxide was added in portions to the warmed solution until the colour was discharged. The solution was finally boiled for 10 minutes, cooled, and acidified. The precipitated acid (45 mg.) had m. p. 274—278°, depressed by about 30° when mixed with acid (V). Esterification with diazomethane gave the *trimethyl* ester of 4 : 5-dicarboxy-9 : 10-dihydrophenanthr-9:10-yleneacetic acid (VIII), which crystallised from light petroleum (b. p. 80—100°) in somewhat discoloured polyhedra, m. p. 175—176° (Found : C, 68·9; H, 5·3; OMe, 25·2. $C_{21}H_{18}O_6$ requires C, 68·8; H, 4·95; OMe, 25·4%).

This work was carried out during the tenure of an I.C.I. Research Fellowship (by G. M. B.) and a Maintenance Allowance awarded by the Department of Scientific and Industrial Research (to A. R. M. G.). We express our thanks for these, and to Mr. J. M. L. Cameron and Miss R. H. Kennaway for microanalyses.

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765. *Synthesis of Certain Trifluoromethyldiphenyl Derivatives.*

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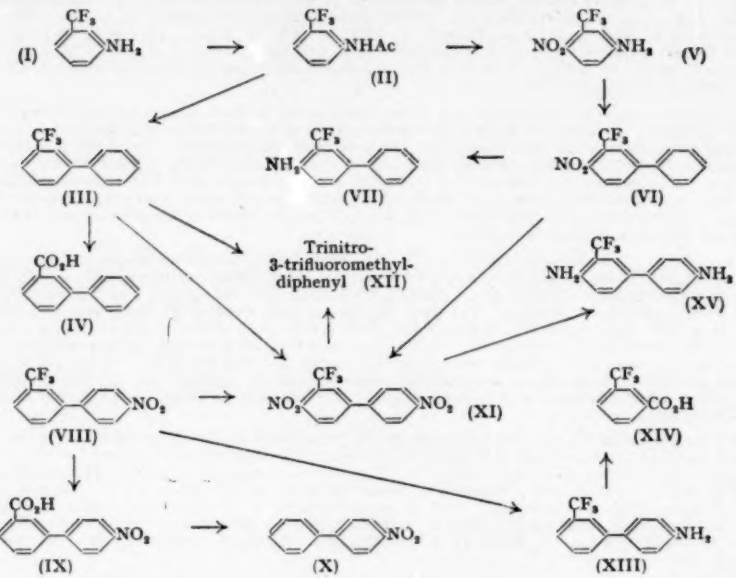
A series of diphenyl derivatives containing trifluoromethyl groups has been prepared. It includes 3-trifluoromethyldiphenyl and certain derived nitro- and amino-compounds, together with some symmetrical dinitro- and diamino-bistrifluoromethyldiphenyls.

THE chemistry of trifluoromethylbenzene derivatives has been studied fairly extensively since the parent compound, benzotrifluoride, was first prepared by Swarts (*Bull. Acad. roy. Belg.*, 1898, [iii], **35**, 375). There have been, however, few references to trifluoromethyldiphenyl compounds. Zahn and Schimmelschmidt (Fr. P. 739,053) mentioned the production of 2 : 5-dimethoxy-3′-trifluoromethyldiphenyl and of its 4-nitro- and 4-amino-derivatives, and Bradsher and Bond (*J. Amer. Chem. Soc.*, 1949, **71**, 2659) recently described the preparation of a number of diphenyls containing trifluoromethyl groups, including 3-trifluoromethyl-, 3 : 3′-bistrifluoromethyl-,

and 2 : 2′-dinitro-4 : 4′-bistrifluoromethyl-diphenyl. As part of the general study of fluoro-organic compounds in progress in this Department, a series of unsymmetrical and symmetrical trifluoromethyldiphenyls has been made, and some of this work is reported herein.

By the formation, from an acetylated aromatic amine, of the corresponding *N*-nitroso-derivative and reaction of the latter with benzene (Bamberger, *Ber.*, **1897**, **30**, 366; Grieve and Hey, *J.*, **1934**, 1797; Haworth and Hey, *J.*, **1940**, 361), 3-trifluoromethyldiphenyl (III) was prepared from *m*-acetamidobenzotrifluoride (II). Alternative methods of synthesis of unsymmetrical diphenyls (see the summary by Bachmann and Hoffman, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, **1944**, p. 224) gave poorer yields of 3-trifluoromethyldiphenyl (III) from diazotised *m*-aminobenzotrifluoride (I).



In conformity with Le Fave's observations (*J. Amer. Chem. Soc.*, **1949**, **71**, 4148) that compounds with trifluoromethyl groups attached to a benzene ring are converted into carboxylic acids by being heated with concentrated sulphuric acid, it was found that 3-trifluoromethyldiphenyl (III), treated in this way, gave diphenyl-3-carboxylic acid (IV), though in addition a proportion of a sulphur-containing product, probably a sulphonic acid, was isolated.

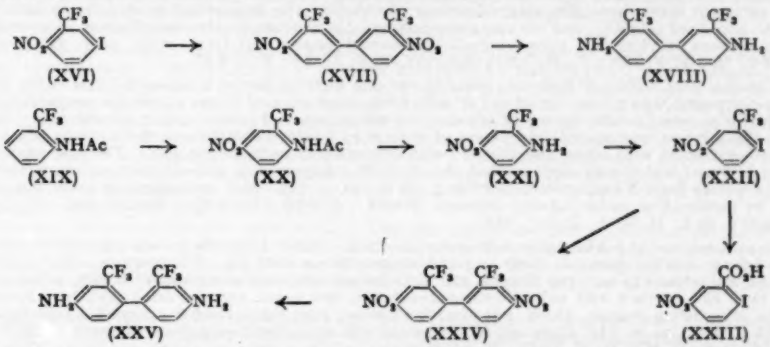
4-Nitro-3-trifluoromethyldiphenyl (VI) was best prepared by diazotisation of 5-amino-2-nitrobenzotrifluoride (V) (Rouche, *Bull. Acad. roy. Belg., Classe Sci.*, **1927**, **13**, 346) and subsequent reaction with benzene in the presence of sodium acetate, according to the method of Elks, Haworth, and Hey (*J.*, **1940**, 1284). Reduction of this nitro-compound (VI) gave 4-amino-3-trifluoromethyldiphenyl (VII).

By treatment of 3-trifluoromethyldiphenyl (III) with nitric–sulphuric acid mixtures a dinitro-3-trifluoromethyldiphenyl (XI) and a trinitro-3-trifluoromethyldiphenyl (XII) were formed. Mononitration was effected with a mixture of nitric, sulphuric, and acetic acids under carefully controlled conditions, though with nitric–acetic acid mixtures, under conditions which effect mononitration of diphenyl itself, there was no reaction. The mononitro-compound (VIII) could be prepared also by treatment of 3-trifluoromethyldiphenyl (III) with a mixture of nitric acid and trifluoroacetic anhydride, which is an active nitrating mixture (Bourne, Stacey, Tatlow, and Tedder, unpublished results). The derivative (VIII) was shown to be 4-nitro-3′-trifluoromethyldiphenyl by the following reactions. With concentrated sulphuric acid (Le Fave, *loc. cit.*) a nitrodiphenylcarboxylic acid (IX) was obtained, and this on decarboxylation yielded 4-nitrodiphenyl (X). Reduction of the nitro-3-trifluoromethyldiphenyl (VIII) with tin and hydro-

chloric acid gave the corresponding amino-3-trifluoromethyldiphenyl (XIII) which, on oxidation with potassium permanganate by a method similar to that which gives trifluoroacetic acid from 3-aminobenzotrifluoride (Haworth and Stacey, B.P. 625,098), gave benzotrifluoride-3-carboxylic acid (XIV). Thus, since the oxidation showed that the amino- and trifluoromethyl groups were substituted in different rings, the compounds must have been 4-nitro-3′-trifluoromethyldiphenyl (VIII) and 4-amino-3′-trifluoromethyldiphenyl (XIII).

The dinitro-3-trifluoromethyldiphenyl (XI) formed by direct nitration of 3-trifluoromethyldiphenyl was also the product of mononitration of both 4-nitro-3′-trifluoromethyldiphenyl (VIII) and 4-nitro-3-trifluoromethyldiphenyl (VI) and hence was 4 : 4′-dinitro-3-trifluoromethyldiphenyl. Reduction with tin and hydrochloric acid gave 4 : 4′-diamino-3-trifluoromethyldiphenyl (XV).

The trinitro-compound (XII) prepared from 3-trifluoromethyldiphenyl was formed also by further nitration of 4 : 4′-dinitro-3-trifluoromethyldiphenyl and so the positions of two of the nitro-groups are established, but the location of the third is not known at present.



Symmetrical diphenyls were made by the Ullmann reaction (Ullmann and Bielecki, *Ber.*, 1901, **34**, 2174). 5-Iodo-2-nitrobenzotrifluoride (XVI), prepared by Jones's method (*J. Amer. Chem. Soc.*, 1947, **69**, 2346), gave, on treatment with copper bronze, 4 : 4′-dinitro-3 : 3′-bistrifluoromethyldiphenyl (XVII), which was reduced to the corresponding benzidine derivative (XVIII).

Nitration of *o*-acetamidobenzotrifluoride (XIX) (Rouche, *loc. cit.*; Jones, *loc. cit.*) gave the expected 5-nitro-derivative (XX), from which there was obtained, after hydrolysis, 2-amino-5-nitrobenzotrifluoride (XXI), and thence by a diazo-reaction 2-iodo-5-nitrobenzotrifluoride (XXII). The structure of this, and hence those of the intermediate compounds, were proved by conversion with sulphuric acid into the known 2-iodo-5-nitrobenzoic acid (XXIII). With copper bronze 2-iodo-5-nitrobenzotrifluoride (XXII) gave 4 : 4′-dinitro-2 : 2′-bistrifluoromethyldiphenyl (XXIV) which on reduction afforded the 4 : 4′-diamine (XXV), identical with that obtained from 3-nitrobenzotrifluoride by conversion into the corresponding hydrazo-derivative and rearrangement of this with mineral acid (Cartwright and Tatlow, unpublished work).

Further aspects of the chemistry of trifluoromethyldiphenyls are being studied, in order to investigate the influence of trifluoromethyl groups on the reactions of aromatic compounds.

Experimental.

Preparation of 3-Trifluoromethyldiphenyl.—*m*-Acetamidobenzotrifluoride (20·0 g.) was dissolved in glacial acetic acid (100 c.c.) and nitrous fumes were passed into the stirred solution at 10° for *ca.* 4 hours until a deep clear green solution was obtained. The liquid was then poured into ice-cold water (500 c.c.) with vigorous stirring, and the yellowish precipitate of the *N*-nitroso-derivative was removed by filtration, and, after being washed with water, was dried on a porous plate. The solid was dissolved in benzene (150 c.c.), and the solution, together with the benzene extracts (2 × 50 c.c.) of the aqueous phase, was stirred at room temperature for 20 hours. There was gradual evolution of nitrogen and the solution became deep red. After removal of the excess of benzene by distillation, the residue was distilled and, in order to hydrolyse any unchanged *m*-acetamidobenzotrifluoride, the distillate was refluxed for 2 hours with concentrated hydrochloric acid (10·0 c.c.), water (10·0 c.c.), and ethyl alcohol (10·0 c.c.). The mixture was distilled to remove alcohol and then extracted exhaustively with ether. The ethereal extracts were dried ($MgSO_4$) and filtered, the ether removed by distillation, and the residue distilled under reduced pressure. The fraction, b. p. 117—120°/13 mm., was recrystallised from ethyl alcohol

containing a few drops of water, to give colourless plates of 3-trifluoromethyldiphenyl (7·0 g., 35%), m. p. 26—27°, b. p. 117—120°/13 mm., n_D^{20} 1·5304 (Found: C, 70·4; H, 4·0; F, 25·2. Calc. for $C_{13}H_9F_3$: C, 70·3; H, 4·1; F, 25·6%). Bradsher and Bond (*loc. cit.*) gave b. p. 118—119°/13 mm. and n_D^{24} 1·5302 for this compound. *m*-Aminobenzotrifluoride (1·6 g.) was isolated from the aqueous residues of the hydrolysis.

Conversion of 3-Trifluoromethyldiphenyl into Diphenyl-3-carboxylic Acid.—3-Trifluoromethyldiphenyl (1·00 g.) and concentrated sulphuric acid (0·35 c.c.) were heated to 130° for 2 hours with stirring. After being cooled, the mixture was poured into aqueous sodium hydroxide and the aqueous phase was filtered, extracted with ether, and then acidified with concentrated hydrochloric acid. The precipitated acid was filtered off and twice recrystallised from aqueous ethyl alcohol, to give diphenyl-3-carboxylic acid (0·209 g., 23%), m. p. 164° (Found: C, 78·8; H, 5·2. Calc. for $C_{13}H_{10}O_2$: C, 78·8; H, 5·1%). Repetition of this experiment gave, in addition to the desired product, varying proportions of a water-soluble compound containing sulphur, probably a sulphonic acid. Jacobson and Lischke (*Ber.*, 1895, **28**, 2541) gave m. p. 166° for diphenyl-3-carboxylic acid.

Mononitration of 3-Trifluoromethyldiphenyl.—3-Trifluoromethyldiphenyl (2·43 g.) was refluxed for 30 minutes with glacial acetic acid (3·00 c.c.), fuming nitric acid (0·90 c.c.; *d* 1·5), and concentrated sulphuric acid (0·60 c.c.). The mixture was then poured into water (20.0 c.c.), and the aqueous phase was extracted with ether. The ethereal extract was washed with sodium hydroxide solution, then with water, and dried ($MgSO_4$), and the ether was removed by distillation. Recrystallisation of the residue from aqueous ethyl alcohol gave *4-nitro-3′-trifluoromethyldiphenyl* (1·74 g., 60%), m. p. 86° (Found: C, 58·6; H, 3·3; F, 20·9. $C_{13}H_8O_2NF_3$ requires C, 58·4; H, 3·0; F, 21·3%).

Conversion of 4-Nitro-3′-trifluoromethyldiphenyl into 4-Nitrodiphenyl-3′-carboxylic Acid.—The above nitro-compound (0·64 g.) was stirred at 110° with 100% sulphuric acid (0·50 c.c.) and the temperature was gradually increased to 150° during 45 minutes, the nitro-compound slowly passing into solution. When cool, the mixture was poured into excess of sodium hydroxide solution, and the aqueous phase was filtered, extracted with ether, and acidified with concentrated hydrochloric acid. The precipitate was filtered off and boiled with ethyl alcohol, the alcoholic solution being then filtered and evaporated, to give *4-nitrodiphenyl-3′-carboxylic acid* (0·39 g., 67%), m. p. 229—231° unchanged by recrystallisation and by sublimation under reduced pressure (Found: C, 64·2; H, 3·8%; Equiv., 247. $C_{13}H_9O_4N$ requires C, 64·2; H, 3·7%; Equiv., 243).

Decarboxylation of 4-Nitrodiphenyl-3′-carboxylic Acid.—This acid (0·099 g.) was refluxed for 6 hours with freshly distilled quinoline (1·00 c.c.) and copper bronze (0·05 g.). The mixture, when cool, was diluted with ether (25 c.c.) and filtered, and the ethereal solution was washed with 50% hydrochloric acid (4 × 25 c.c.), then with sodium hydroxide solution, and water, and was dried ($MgSO_4$). Removal of the ether left a residue, which, after recrystallisation from ethyl alcohol, afforded 4-nitrodiphenyl (0·050 g., 62%), m. p. 114° alone and in admixture with an authentic specimen (Found: C, 72·1; H, 4·8. Calc. for $C_{12}H_9O_2N$: C, 72·35; H, 4·55%).

Preparation of 4-Amino-3′-trifluoromethyldiphenyl.—4-Nitro-3′-trifluoromethyldiphenyl (2·48 g.) was heated under reflux for 3 hours with concentrated hydrochloric acid (15·0 c.c.), ethyl alcohol (5·0 c.c.), and granulated tin (10·0 g.). The liquid was filtered and evaporated to remove the alcohol. It was then made alkaline with sodium hydroxide solution and extracted with ether. The ethereal extracts were washed with water and then dried ($MgSO_4$), and the ether was removed by distillation. Recrystallisation of the crude product from aqueous ethyl alcohol afforded *4-amino-3′-trifluoromethyldiphenyl* (1·89 g., 86%), m. p. 65° (Found: C, 65·7; H, 4·0; F, 24·0. $C_{13}H_{10}NF_3$ requires C, 65·8; H, 4·2; F, 24·0%).

Treatment of the amine with benzoyl chloride and aqueous sodium hydroxide gave the *benzoyl* derivative, m. p. 195—196°, which crystallised from ethyl alcohol (Found: C, 70·2; H, 4·3. $C_{20}H_{14}ONF_3$ requires C, 70·4; H, 4·1%).

Oxidation of 4-Amino-3′-trifluoromethyldiphenyl.—The amine (0·351 g.) was added gradually and with rapid stirring to a mixture of potassium permanganate (3·05 g.), water (5·0 c.c.), and concentrated sulphuric acid (2·0 c.c.) at 50°. When the addition was complete, the mixture was stirred at 100° for 1 hour. Water (30 c.c.) was added and a stream of sulphur dioxide was passed through the mixture until all the manganese dioxide had dissolved. The whole was then extracted exhaustively with ether. The ethereal extracts were shaken with sodium hydroxide solution and the aqueous phase was separated from the ether, acidified with concentrated hydrochloric acid, and extracted with ether. These ethereal extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue, after two recrystallisations from carbon tetrachloride, afforded benzotrifluoride-3-carboxylic acid (0·107 g., 38%), m. p. 104° alone and in admixture with an authentic specimen (Found: C, 50·6; H, 2·7. Calc. for $C_8H_5O_2F_3$: C, 50·5; H, 2·6%). Swarts (*loc. cit.*) cited m. p. 103° for this compound.

Preparation of 4:4′-Dinitro-3-trifluoromethyldiphenyl.—(*a*) 4-Nitro-3′-trifluoromethyldiphenyl (0·275 g.), glacial acetic acid (0·30 c.c.), fuming nitric acid (0·10 c.c.), and concentrated sulphuric acid (0·07 c.c.) were gently refluxed for ½ hour. When cool, the mixture was poured into water, and the precipitate was filtered off, washed, and recrystallised from aqueous ethyl alcohol to give *4:4′-dinitro-3-trifluoromethyldiphenyl* (0·190 g., 59%), m. p. 180—181°, alone or in admixture with the material obtained as in (*b*) (Found: C, 50·1; H, 2·3; F, 18·2. $C_{13}H_7O_4N_2F_3$ requires C, 50·0; H, 2·3; F, 18·3%).

(*b*) 4-Nitro-3-trifluoromethyldiphenyl (1·120 g.), treated as above with glacial acetic acid (1·50 c.c.), fuming nitric acid (0·35 c.c.), and concentrated sulphuric acid (0·40 c.c.), gave the same dinitro-derivative (1·128 g., 86%), m. p. 181°.

(*c*) The same product was produced by nitration of 3-trifluoromethyldiphenyl under similar conditions.

Preparation of 4 : 4′-*Diamino*-3-*trifluoromethyldiphenyl*.—4 : 4′-Dinitro-3-trifluoromethyldiphenyl (0·806 g.) was heated under reflux with concentrated hydrochloric acid (10·0 c.c.), ethyl alcohol (3·0 c.c.), and granulated tin (10·0 g.). After working up as in the case of the 4-amino-3′-trifluoromethyl derivative there was obtained 4 : 4′-*diamino*-3-*trifluoromethyldiphenyl* (0·578 g., 89%), m. p. 86° (Found : C, 61·7; H, 4·5; F, 22·2. $C_{13}H_{11}N_2F_3$ requires C, 61·9; H, 4·4; F, 22·6%).

This amine, on treatment with a mixture of acetic acid and acetic anhydride, yielded the *diacetyl* derivative, m. p. 285—286° after recrystallisation from ethyl alcohol (Found : C, 61·0; H, 4·5. $C_{17}H_{15}O_2N_2F_3$ requires C, 60·7; H, 4·5%).

With benzoyl chloride and sodium hydroxide solution the amine gave the *dibenzoyl* derivative, m. p. 286—287° after recrystallisation from ethyl alcohol (Found : C, 70·4; H, 4·1. $C_{27}H_{19}O_2N_2F_3$ requires C, 70·4; H, 4·2%).

Preparation of Trinitro-3-*trifluoromethyldiphenyl*.—(*a*) 3-Trifluoromethyldiphenyl (5·79 g.) was refluxed for 40 minutes with a mixture of concentrated nitric acid (15·0 c.c.) and concentrated sulphuric acid (20·0 c.c.). The reaction mixture, treated as in the case of 4-nitro-3′-trifluoromethyldiphenyl, afforded *trinitro*-3-*trifluoromethyldiphenyl* (5·60 g., 60%), m. p. 153·5—154·5° (Found : C, 43·8; H, 1·6; F, 15·8. $C_{13}H_6O_6N_3F_3$ requires C, 43·7; H, 1·7; F, 16·0%).

(*b*) 4 : 4′-Dinitro-3-trifluoromethyldiphenyl (0·235 g.), refluxed for 2 hours with concentrated nitric acid (1·0 c.c.) and concentrated sulphuric acid (1·0 c.c.), gave the same product (0·238 g., 89%), m. p. 153—154° alone or in admixture with the specimen mentioned above.

Preparation of 4-*Nitro*-3-*trifluoromethyldiphenyl*.—5-Amino-2-nitrobenzotrifluoride (Jones, *loc. cit.*) (13·1 g.) was treated at 5° with concentrated sulphuric acid (7·0 c.c.), water (13·0 c.c.), and a solution of sodium nitrite (4·7 g.) in water (8·0 c.c.). The filtered diazonium solution was stirred for 1 hour at 0—5° with benzene (100 c.c.) whilst a solution of sodium acetate trihydrate (50·0 g.) in water (150 c.c.) was added dropwise, and then the mixture was stirred for a further 2 hours at 0—5° and for 15 hours at room temperature. The benzene layer was separated, washed, dried ($MgSO_4$), and distilled to remove the benzene, the residue being distilled under diminished pressure. The fraction having b. p. 123—128°/0·3 mm. (3·8 g., 22%) crystallised on storage and was 4-*nitro*-3-*trifluoromethyldiphenyl*, m. p. 30·5—31·5° (unchanged by recrystallisation from aqueous ethyl alcohol) (Found : C, 58·3; H, 3·3; F, 20·9. $C_{13}H_8O_2NF_3$ requires C, 58·4; H, 3·0; F, 21·3%).

Reduction of 4-*Nitro*-3-*trifluoromethyldiphenyl*.—This nitro-compound (2·00 g.), reduced as described for the 4-nitro-3′-trifluoromethyl isomer, yielded, after recrystallisation of the crude product from aqueous ethyl alcohol, 4-*amino*-3-*trifluoromethyldiphenyl* (1·49 g., 84%), m. p. 61·5°, depressed by the 4-amino-3′-trifluoromethyl isomer (Found : C, 65·6; H, 4·2; F, 23·7. $C_{13}H_{10}NF_3$ requires C, 65·8; H, 4·2; F, 24·0%).

Treatment of the amine in ethereal solution with dry hydrogen chloride gave the *amine hydrochloride*, m. p. 134—135° [Found : C, 57·2; H, 4·0%; Equiv. (by titration with sodium hydroxide), 273·0. $C_{13}H_{11}NClF_3$ requires C, 57·05; H, 4·05%; Equiv., 273·7].

The amine gave, with acetic acid–acetic anhydride an *acetyl* derivative, m. p. 160—161° (Found : C, 64·3; H, 4·1; F, 20·4. $C_{15}H_{12}ONF_3$ requires C, 64·5; H, 4·3; F, 20·4%), and with benzoyl chloride–sodium hydroxide a *benzoyl* derivative, m. p. 168·5—169·5° (Found : C, 70·2; H, 4·2; F, 16·2. $C_{20}H_{14}ONF_3$ requires C, 70·4; H, 4·1; F, 16·7%).

Preparation of 4 : 4′-*Dinitro*-3 : 3′-*bistrifluoromethyldiphenyl*.—5-Iodo-2-nitrobenzotrifluoride (Jones, *loc. cit.*) (3·12 g.) was heated with copper bronze (0·60 g.) for 30 minutes, the temperature being increased gradually from 265° to 300°. When cool, the mixture was extracted with boiling benzene and after filtration and distillation to remove the benzene, the residue was recrystallised from aqueous ethyl alcohol and then twice from aqueous acetone, to give 4 : 4′-*dinitro*-3 : 3′-*bistrifluoromethyldiphenyl* (0·65 g., 35%), m. p. 181—182° (Found : C, 44·3; H, 1·5; F, 29·5. $C_{14}H_6O_4N_2F_6$ requires C, 44·2; H, 1·6; F, 30·0%).

Preparation of 4 : 4′-*Diamino*-3 : 3′-*bistrifluoromethyldiphenyl*.—4 : 4′-Dinitro-3 : 3′-bistrifluoromethyldiphenyl (0·815 g.), reduced as before with tin and aqueous alcoholic hydrochloric acid yielded, after three recrystallisations of the product from aqueous ethyl alcohol, 4 : 4′-*diamino*-3 : 3′-*bistrifluoromethyldiphenyl* (0·602 g., 88%), m. p. 115—116·5° (Found : C, 52·5; H, 3·2; F, 35·2. $C_{14}H_{10}N_2F_6$ requires C, 52·5; H, 3·1; F, 35·6%).

Treatment of an ethereal solution of this amine with trifluoroacetic anhydride gave the *bistrifluoroacetyl* derivative, m. p. 202° (Found : C, 42·1; H, 1·8. $C_{18}H_8O_4N_2F_{12}$ requires C, 42·2; H, 1·6%).

Preparation of 2-*Amino*-5-*nitrobenzotrifluoride*.—*o*-Acetamidobenzotrifluoride (Jones, *loc. cit.*) (2·98 g.) was added slowly and with stirring to concentrated sulphuric acid (16·5 c.c.) cooled to 0°, and then a mixture of fuming nitric acid (0·80 c.c.; *d* 1·5) and concentrated sulphuric acid (1·5 c.c.) was added. After being kept for 15 minutes at 0° and for 30 minutes at 15°, the mixture was heated to 40° for 15 minutes, becoming golden-yellow, and was then poured slowly on crushed ice. The precipitate was collected by filtration, dried, and recrystallised from ethyl alcohol, to give 2-*acetamido*-5-*nitrobenzotrifluoride* (2·81 g., 77%), m. p. 148° (Found : C, 43·9; H, 2·9; F, 23·0. $C_9H_7O_3N_2F_3$ requires C, 43·6; H, 2·8; F, 23·0%).

Hydrolysis of this compound (5·94 g.) with sodium hydroxide (3·0 g.) in water (15·0 c.c.) and ethyl alcohol (8·0 c.c.) gave, after recrystallisation of the crude product from benzene–light petroleum (b. p. 60—80°), 2-amino-5-nitrobenzotrifluoride (4·13 g., 84%), m. p. 94° (Found : C, 40·9; H, 2·5; F, 27·6; Calc. for $C_7H_4O_2N_2F_3$: C, 40·8; H, 2·4; F, 27·7%). Daudt and Woodward (U.S.P. 2,194,926) gave m. p. "about 88°."

Conversion of 2-*Amino*-5-*nitrobenzotrifluoride into* 2-*Iodo*-5-*nitrobenzotrifluoride*.—The amine (5·70 g.), dissolved in a mixture of glacial acetic acid (25·0 c.c.) and concentrated sulphuric acid (5·0 c.c.), was

diazotised at 0° with sodium nitrite (2·5 g.) in water (5·0 c.c.). The solution was poured into potassium iodide (15·0 g.) dissolved in water (50·0 c.c.) and, after 3 hours, the precipitate was filtered off, distilled in steam and recrystallised from aqueous ethyl alcohol. The product, *2-iodo-5-nitrobenzotrifluoride* (7·21 g., 82%), had m. p. 82° (Found: C, 26·4; H, 1·0; F, 17·6. $C_7H_3O_2INF_3$ requires C, 26·5; H, 1·0; F, 18·0%).

Conversion of 2-Iodo-5-nitrobenzotrifluoride into 2-Iodo-5-nitrobenzoic Acid.—The iodo-derivative (0·36 g.) was stirred at 120—130° for 1½ hours with 100% sulphuric acid (0·80 c.c.). When cool, the solution was poured into water, and the aqueous phase was extracted with ether. The ethereal extracts, after being washed with water, were shaken with aqueous sodium hydroxide which was separated, acidified, and ether-extracted. The second ethereal extracts were washed with water and dried ($MgSO_4$). The ether was removed by distillation and the residue on recrystallisation from water afforded 2-iodo-5-nitrobenzoic acid (0·109 g., 33%), m. p. 193—195° (alone or in admixture with an authentic specimen prepared by the method of Goldstein and Grampoloff, *Helv. Chim. Acta*, 1930, **13**, 310) (Found: C, 28·6; H, 1·1. Calc. for $C_7H_4O_4IN$: C, 28·7; H, 1·4%).

Ullmann Reaction on 2-Iodo-5-nitrobenzotrifluoride.—The iodo-compound (3·57 g.) was heated with copper bronze (1·90 g.) for 30 minutes at 250—300°. After isolation as before, the product, *4 : 4′-dinitro-2 : 2′-bistrifluoromethyldiphenyl* (0·362 g., 17%), had m. p. 137·5° (Found: C, 44·2; H, 1·5; F, 29·7. $C_{14}H_6O_4N_2F_6$ requires C, 44·2; H, 1·6; F, 30·0%).

Preparation of 4 : 4′-Diamino-2 : 2′-bistrifluoromethyldiphenyl.—The corresponding dinitro-derivative (0·173 g.), treated as in the case of 4-nitro-3′-trifluoromethyldiphenyl, gave, after recrystallisation of the crude product from aqueous ethyl alcohol, *4 : 4′-diamino-2 : 2′-bistrifluoromethyldiphenyl* (0·125 g., 86%), m. p. 182° (Found: C, 52·6; H, 3·3; F, 35·7. $C_{14}H_{10}N_2F_6$ requires C, 52·5; H, 3·1; F, 35·6%). The m. p. of this compound was not depressed in admixture with the product obtained by acid treatment of the hydrazo-derivative prepared from 3-nitrobenzotrifluoride (Cartwright and Tatlow, unpublished results).

The authors express their gratitude to Professor M. Stacey, F.R.S., for his interest in this work. They are indebted also to Mr. B. S. Noyes for the analyses and to Mr. A. M. Hunt for experimental assistance.

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[*Received, August 30th*, 1951.]

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766. *Chemical Constitution and Amœbicidal Action. Part I. Synthesis of α-Tetrahydroisoquinolino-ω-tetrahydro-1-isoquinolylalkanes Related to Emetine.*

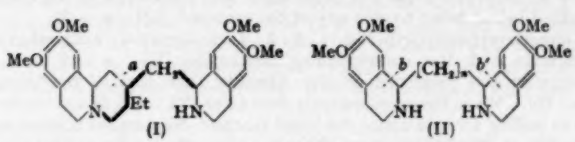
By J. M. OSBOND.

Some analogues of emetine, chiefly certain α-tetrahydro*iso*quinolino-ω-tetrahydro-1-*iso*quinolylalkanes (VIII), have been prepared which contain secondary and tertiary basic centres as present in emetine (I), in an attempt to discover what part of the emetine molecule is necessary for biological activity. These compounds have been synthesised by the route (IV) ⟶ (VIII). Although active, they do not compare favourably with emetine *in vitro*.

EMETINE is unique and specific in its action on *Entamœba histolytica*, the protozoon responsible for amœbic dysentery (Dobell and Laidlaw, *Parasit.*, 1926, **18**, 206; Dobell, *Ann. Soc. belg. Med. trop., Liber Jubilaris J. Rodhain*, 1947, 201). It has the highest known activity *in vitro* of any compound which still retains its activity *in vivo* and has been used clinically for several centuries in various forms. However, although emetine still retains its pre-eminence over other drugs, there is a need for more effective and less toxic amœbicidal agents.

The correct structure for emetine (I) was put forward by Robinson (*Nature*, 1948, **162**, 524) on biogenetic grounds and confirmed independently by Battersby and Openshaw (*J.*, 1949, S59, S67, 3207) and Pailer *et al.* (*Monatsh.*, 1948, **78**, 331, 348; **79**, 127; 1949, **80**, 94) by degradative studies and by the synthesis of (±)-rubremetinium bromide (Battersby and Openshaw, *Experientia*, 1950, **6**, 378). Earlier, the preparation of analogues of emetine had been based on the old emetine formula of Brindley and Pyman (*J.*, 1927, 1067). Thus Child and Pyman (*J.*, 1929, 2010) synthesised a series of αω-bistetrahydro-1-*iso*quinolylalkanes (II; $n = 4$ and 5) and αω-bisdihydro-1-*iso*quinolylalkanes (XIII; $n = 2$, 3, and 6, R = H), but these compounds were devoid of activity. Goodson, Goodwin, Gorvin, Goss, Kirby, Lock, Neal, Sharp, and Solomon (*Brit. J. Pharmacol.*, 1948, **3**, 49) developed this line by preparing bis-[2-

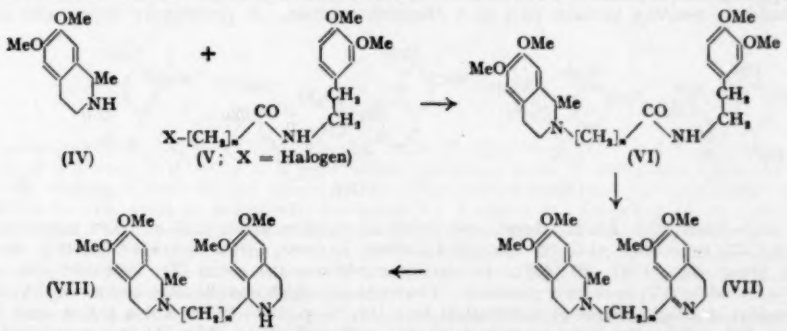
(3 : 4-dimethoxyphenyl)ethylamino]alkanes (rupture of II at *b* and *b'*); several of these compounds exhibited a marked activity both *in vitro* and *in vivo*. They also prepared certain other simple compounds formally derived from emetine, of the bisalkylaminoalkane type which linked



up with a series previously explored by Pyman (*J. Soc. Chem. Ind.*, 1937, **56**, 789) ending in the discovery by Pyman of bisdiamylaminodecane, which was considered to be more active *in vitro* than emetine (cf., however, Goodson and his collaborators, *ibid.*, p. 62); it was, however, not successful clinically. Child and Pyman (*J.*, 1931, 36) have also prepared the benzopyrrocoline (III; $n = 1$) and the corresponding benzopyridocoline (III; $n = 2$) which were inactive (cf. also Sugasawa *et al.*, *Ber.*, 1941, **74**, 455, 537; *Proc. Imp. Acad., Tokyo*, 1939, **15**, 82; *J. Pharm. Soc. Japan*, 1949, **69**, 85; King and Robinson, *J.*, 1938, 2119; Hall, Mahboob, and Turner, *J.*, 1950, 1842).

The present work describes the preparation of certain α-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)-ω-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-*iso*quinolyl)alkanes (VIII) which may be regarded as being derived from the emetine molecule (I) by rupture of the bond at *a*, thus linking the two tetrahydro*iso*quinolyl nuclei by a carbon chain, as shown in (I) by heavy bonds. These dibasic compounds contain secondary and tertiary nitrogen atoms, which are present in emetine, separated by a varying number of carbon atoms. It was felt desirable to retain the four methoxy-substituents in these analogues since these groups not only often confer enhanced biological activity but also greatly facilitate ring closure in the Bischler-Napieralski reaction.

The route chosen for the synthesis of these compounds was as shown in the scheme (IV) ⟶ (VIII). The *N*-[2-(3 : 4-dimethoxyphenyl)ethyl]-ω-halogeno-acid amides (V; $n = 1$, 2, 4, 5, or 10) were prepared by addition of the appropriate ω-halogeno-acid chloride to 2-(3 : 4-dimethoxyphenyl)ethylamine in ether (cf. Child and Pyman, *loc. cit.*, 1931). 1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinoline [IV; (±)-salsolidine] was prepared by the cyclisation of *N*-[2-(3 : 4-dimethoxyphenyl)ethyl]acetamide with phosphoric oxide in toluene (Spath and Polgar, *Monatsh.*, 1929, **51**, 190) followed by reduction of the dihydro*iso*quinoline with palladised strontium carbonate (cf. Spath and Dengel, *Ber.*, 1938, **71**, 113); it was condensed with the ω-halogeno-amide (V) in benzene in the presence of potassium carbonate, to give *N*-[2-(3 : 4-dimethoxyphenyl)ethyl]-ω-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*-quinolino)-amides (VI; $n = 1$, 2, 4, 5, and 10). The condensation proceeded smoothly between (IV) and (V; $n = 1$, 4, 5, or 10) although in the case of (VI; $n = 5$) neither the base nor a salt could be obtained crystalline. In the preparation of (VI; $n = 2$), obtained in only moderate

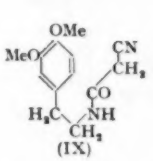


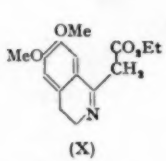
yield, it was at first difficult to obtain the pure crystalline hydrochloride and recourse was had to fractional extraction of a solution of the hydrochloride with alkali and ether. The ω-bromobutyramide (V; $n = 3$, X = Br) is not stable (cf. Child and Pyman, *loc. cit.*, 1931) and in the

presence of moisture decomposes readily to 2-(3 : 4-dimethoxyphenyl)ethylamine hydrobromide and butyrolactone. An attempt was therefore made to prepare the bromo-amide (V; $n = 3$, X = Br) in benzene and condense it directly with (±)-salsolidine (IV). The tetrahydro*iso*quinolylbutyramide (VI; $n = 3$), however, could not be isolated, and cyclisation of the crude material by the method described below failed to give any of the required (VII; $n = 3$).

Cyclisation of *N*-[2-(3 : 4-dimethoxyphenyl)ethyl]-β-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)propionamide and the corresponding acetamide (VI; $n = 2$ and 1 respectively) was first investigated and presented greater difficulty than that of the higher homologues (VI; $n = 4$, 5, and 10). When the propionamide derivative (VI; $n = 2$) was treated with phosphorus oxychloride in boiling toluene under the usual Bischler–Napieralski conditions, or with phosphorus pentachloride in chloroform at room temperature (Gulland and Haworth, *J.*, 1928, 581, 2083), only an amorphous product resulted from which no crystalline salt could be obtained. The acetamido-derivative (VI; $n = 1$) was also sensitive to cyclisation using the Gulland–Haworth modification at room temperature, but a small quantity of the required bis*iso*quinoline derivative (VII; $n = 1$) was obtained; when the reaction was carried out at −5° and then at 0°, a 42% yield of the desired product was obtained. Although this method was successful on two occasions, some difficulty was encountered on two subsequent runs, conducted under what were considered to be identical conditions, when a certain amount of gummy material prevented crystallisation, but after chromatography of the crude base on alumina the required salt was obtained crystalline although in diminished yield. The methane base (VII; $n = 1$) appeared to combine with only 1·5 molecules of hydrogen bromide, as did the bistetrahydro-compound derived from it by reduction. It is not unusual for dibasic compounds in a homologous series, where the two basic centres are in close proximity, to bind anomalous amounts of hydrogen halide (Mann and Watson, *J. Org. Chem.*, 1948, **13**, 502; Cook and Moffat, *J.*, 1950, 1169; Fulton, Joyner, King, Osbond, and Wright, *Proc. Roy. Soc.*, 1950, *B*, **137**, 356), and certain dihydro*iso*quinolines are known to combine with non-stoicheiometric amounts of acid (Harwood and Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 2555). The other three amides (VI; $n = 4$, 5, and 10) were, by contrast, smoothly cyclised by treatment at room temperature with phosphorus pentachloride in chloroform in good yield without complications, to give the corresponding butane, pentane, and decane derivatives respectively (VII; $n = 4$, 5, and 10).

An alternative method for the synthesis of ethane derivatives such as (VII; $n = 2$) was investigated in the following way. α-Cyano-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]acetamide (IX) was cyclised to 1-cyanomethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline (cf. X; CN for CO_2Et) with phosphoric oxide in toluene in 55% yield and gave on alcoholysis with hydrogen chloride and ethanol ethyl α-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)acetate (X) in almost quantitative yield. After this work had been completed the ester (X) was mentioned in a brief note by Battersby and Openshaw (*Experientia*, 1950, **6**, 378) who prepared it by a different route. When the ester (X) was treated with dilute aqueous alcoholic potassium hydroxide it was cleaved to 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline in good yield. It was considered that the CH_2 group between the two electronegative groups in the ethyl *iso*quinolylacetate (X) would be sufficiently reactive to take part in a Mannich reaction. A preliminary experiment with


(IX)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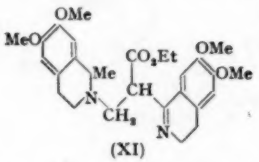
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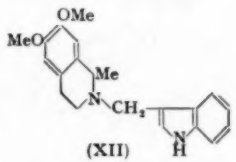
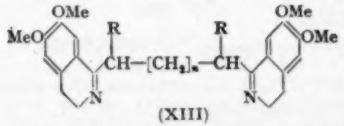
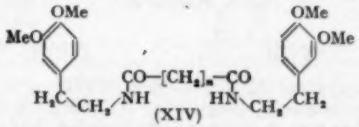

(XII)

(±)-salsolidine (IV), formaldehyde, and indole in aqueous acetic acid at room temperature gave (XII) in *ca.* 40% yield (cf. Craig and Tarbell, *J. Amer. Chem. Soc.*, 1949, **71**, 462; Kuhn and Stein, *Ber.*, 1937, **70**, 567). In similar conditions the ester (X), formaldehyde, and (±)-salsolidine (IV) gave three products: a basic oil (A) which was characterised as the dihydrobromide; a small amount of a colourless base (B), m. p. 183—185°; and a yellow base (C), m. p. 180—181°; the last two were separated with difficulty. Base (A) was considered to be ethyl α-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-β-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)propionate (XI), and hydrogenation revealed one double bond. One of the other products (B) or (C) was thought at first to be bis-(1 : 2 : 3 : 4-tetrahydro-6 : 7-

dimethoxy-1-methyl*iso*quinolino)methane (XVI) but an authentic specimen (m. p. 105—107°) prepared by condensing (±)-salsolidine and formaldehyde in aqueous acetic acid, proved to be different. These compounds were therefore derived from the ester (X) and formaldehyde. Analysis indicated that the base (B) could be ethyl αα′-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)glutarate (XIII; $n = 1$, $R = CO_2Et$), and this compound (B) was synthesised in good yield by condensing the ester (X; 2 mols.) with formaldehyde (1 mol.) in aqueous acetic acid. In this condensation a second compound was isolated of m. p. 158—160°, and these two isomers are presumably racemic and *meso*-forms since both gave on alkaline hydrolysis

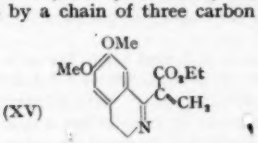


(XIII)

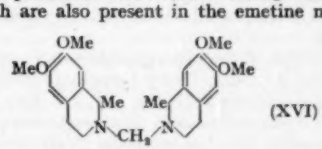


(XIV)

a new base (D), m. p. 162—163° (the former in 77% yield), which was shown to be 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (XIII; $n = 1$, $R = H$). Child and Pyman (*loc. cit.*, 1929) had previously attempted to obtain this analogue of emetine by the cyclisation of *NN′*-[2-(3 : 4-dimethoxyphenyl)ethyl]glutardiamide (XIV; $n = 3$) with phosphorus oxychloride in toluene, but, although this method had been successful with the higher homologues (XIV; $n = 4$, 5, and 8), with (XIV; $n = 3$) they obtained resinous material together with a small amount of a base [characterised as the monohydriodide, and considered to be derived from (XIV; $n = 3$) by cyclisation with loss of one molecule of water] and a quaternary salt derived from it. The cyclisation of (XIV; $n = 3$) has now been re-investigated and, although the use of phosphorus pentachloride in chloroform, which was shown to be successful with (XIV; $n = 4$), or phosphoric oxide in phosphoric acid did not give the required product, phosphoric oxide in toluene gave (XIII; $n = 1$, $R = H$), in 35% yield, identical with base (D) derived from base (B). After removal of a small amount of starting material, the residual gum from this cyclisation partly solidified on protracted storage, to give a second base (E), $C_{25}H_{32}O_3N_2$, in 19% yield. This base was further characterised by a monohydriodide, m. p. 134—135°. It was γ-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]butyramide [formed from (XIV; $n = 3$) by loss of $1H_2O$], although the melting point of our hydriodide differed markedly from that recorded by Child and Pyman (*loc. cit.*, 1929; m. p. 203—204°). Support for this structure was provided by treatment of base (E) with phosphoric oxide in toluene which gave 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (XIII; $n = 1$, $R = H$). Reduction of the propane base (XIII; $n = 1$, $R = H$) with tin and hydrochloric acid gave two isomers, presumably racemic and *meso*-forms of 1 : 3-bis-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (II; $n = 3$) which were separated and characterised as their dihydrobromides. It is of interest that (XIII; $n = 1$, $R = H$) and (II; $n = 3$) have the two *iso*quinoline nuclei linked through the 1 : 1′-positions by a chain of three carbon atoms, which are also present in the emetine molecule



(XV)

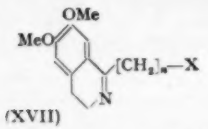


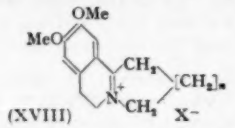
(XVI)

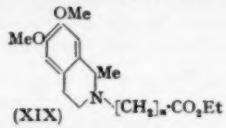
(I); the synthesis (X) ⟶ (XIII; $n = 1$, $R = CO_2Et$) ⟶ (XIII; $n = 1$, $R = H$) or (XIV, $n = 3$) ⟶ (XII; $n = 1$, $R = H$) might provide a route to still closer analogues of emetine and may merit further investigation. The third yellow base (C), which was also obtained in 71% yield by condensing the ester (X; 1 mol.) with formaldehyde (1 mol.) in aqueous acetic acid, could be either the hydroxymethyl or the methylene derivative (XV) of the ester (X) and analysis indicated that (XV) was correct. Dey and Govindachari (*Arch. Pharm.*, 1939, **277**, 177) have shown that 1-cyanomethyl-3 : 4-dihydro-6 : 7-methylenedioxy-*iso*quinoline readily yields benzylidene derivatives.

It was not thought feasible to obtain bis*iso*quinolines (VII) by condensing (±)-salsolidine (IV) directly with the appropriate 1-ω-halogenoalkyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinolines (XVII; X = halogen) since the latter class of compounds are reported to be unstable. For instance, attempts by Child and Pyman (*loc. cit.*, 1931) to condense 1-ω-chloromethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline (XVII; $n = 1$, X = Cl) with ammonia or potassium

phthalimide gave only red amorphous products (cf. also Dey and Govindachari, *loc. cit.*), and our own experience showed that although the base (XVII; $n = 1$, X = Cl) was relatively stable in benzene or ether, attempts to isolate it led to red amorphous products. However, by carefully treating a benzene solution of the base or the hydrochloride of (XVII; $n = 1$; X = Cl) with an excess of piperidine 3 : 4-dihydro-6 : 7-dimethoxy-1-(piperidinomethyl)-


(XVII)


(XVIII)


(XIX)

*iso*quinoline dihydrochloride (XVII; $n = 1$, X = $-N<[CH_2]_5$) was obtained. An attempt to condense (±)-salsolidine (IV) with the 1-chloromethyl*iso*quinoline (XVII; $n = 1$, X = Cl) in benzene in the hope of obtaining (VII; $n = 1$) led to a complex mixture from which no crystalline material could be obtained. It is interesting that the other members of this series (XVII; $n = 2$, 3, and 4, X = halogen) are equally unstable. Child and Pyman (*loc. cit.*, 1931) found that (XVII; $n = 2$, X = Cl) could not be isolated, as it was dehalogenated and polymerised during the cyclisation process (cf., however, Rajagopalan, *Proc. Indian Acad. Sci.*, 1941, **14**, *A*, 126); further (XVII; $n = 3$, X = Cl) spontaneously cyclised to (XVIII; $n = 1$, X = Cl), and (XVII; $n = 4$, X = Cl), although more stable, quaternised when warmed to give (XVIII; $n = 2$, X = Cl). The amides (V; $n = 5$ and 10, X = Br) have now been cyclised to the corresponding ω-bromopentyl- and ω-bromodecyl-3 : 4-dihydro-6 : 7-dimethoxy-*iso*quinolines (XVII; $n = 5$ and 10, X = Br) with phosphorus oxychloride in toluene. The ω-bromopentyl derivative, although more stable than the next lower homologue as might be expected, gives, when refluxed in benzene for one hour, a 34% yield of a quaternary bromide together with 40% recovery of the bromopentyl*iso*quinoline. The quaternary bromide, formulated as (XVIII; $n = 3$, X = Br) gives, on reduction with tin and hydrochloric acid, the hydrobromide of (III; $n = 3$). These two compounds, which contain seven-membered rings, represent a new type of ring system (cf. Sugasawa, Sakurai, and Sugimoto, *Proc. Imp. Acad., Tokyo*, 1939, **15**, 82).

Since, as already mentioned, the bis*iso*quinoline-propane compound (VII; $n = 3$) could not be obtained by the route (IV ⟶ VII), two alternative syntheses were attempted. Ethyl 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolinoacetate (XIX; $n = 1$), prepared by condensing (±)-salsolidine (IV) with ethyl bromoacetate in benzene in the presence of potassium carbonate, was condensed with the ester (X) in the presence of sodium ethoxide, but the only product identified was 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline. Secondly, ethyl γ-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)butyrate (XIX; $n = 3$), prepared in a similar manner from ethyl γ-bromobutyrate, was condensed with some difficulty with 2-(3 : 4-dimethoxyphenyl)ethylamine in an attempt to prepare the amide (VI; $n = 3$), which, however, could not be isolated; and cyclisation of the crude product gave no crystalline material.

Reduction of the bis*iso*quinoline-derivatives (VII; $n = 1$, 4, 5, and 10) to the α-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)-ω-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-*iso*quinolyl)alkanes (VIII; $n = 1$, 4, 5, and 10) was effected catalytically with Adams's catalyst in dilute hydrochloric acid at atmospheric pressure. Although by introducing a second asymmetric centre into the molecule (VII) two racemates should be obtained, in only one case (VIII; $n = 5$) were two distinct isomers isolated and characterised as dihydrogen dioxalates. In the case of the decane derivative (VIII; $n = 10$) a crystalline salt could not be obtained.

The compounds described in this communication have been tested *in vitro* against *E. histolytica* by Dr. J. D. Fulton of this Institute, using the Dobell medium containing the single organism *Bacterium coli* (Dobell, *loc. cit.*). This test has the advantage over the medium containing a mixed bacterial flora (Laidlaw, Dobell, and Bishop, *Parasit.*, 1928, **20**, 207) in that it distinguishes between direct amœbicidal action, as displayed by emetine, and indirect action caused by any bactericidal properties of the drug (cf. Fulton, Joyner, King, Osbond, and Wright, *loc. cit.*; Goodwin, Hoare, and Sharp, *Brit. J. Pharmacol.*, 1948, **3**, 44).

The most promising compound in this series was (VIII; $n = 10$) which was active at 2×10^{-6}; this was not obtained in a crystalline form but was purified by chromatography (see Experimental). Emetine, which was used as a standard in all the tests, was active at 10^{-6} to 2×10^{-7} under the same conditions. Compounds [VIII; $n = 4$ and 5 (both forms)], (VII; $n = 5$ and

10), and (XII) were active at 10^{-4}, and (VIII; $n = 1$) and (VII; $n = 4$) were active between 10^{-3} and 10^{-4}. It was found that (VI; $n = 4$ and 5), (XI), (XIII; $n = 1$, R = H), (XIII; $n = 1$, R = CO_2Et), (IIA; $n = 3$), (XVII; $n = 10$, X = Br; and $n = 1$, X = piperidino) and (X) were active at 10^{-3}; so were (VI; $n = 1$ and 2) and (XIII; $n = 2$, R = H) but these exhibited bactericidal properties at this dilution (*i.e.*, methylene-blue was not reduced). It is of interest that (IIB; $n = 3$), (XVIII; $n = 2$), (III; $n = 2$) and (XVII; $n = 5$, X = Br) were inactive. Most of the other intermediate compounds described have been tested but displayed no marked activity.

Experimental.

6-Bromo-N-[2-(3 : 4-dimethoxyphenyl)ethyl]hexanamide (V; $n = 5$, X = Br).—6-Bromohexanoyl chloride (b. p. 130°/20 mm.; 11·7 g.) in ether (30 c.c.) was added dropwise to 2-(3 : 4-dimethoxyphenyl)-ethylamine (20 g.; Bide and Wilkinson, *J. Soc. Chem. Ind.*, 1945, **64**, 84) in ether (100 c.c.) at 0° with vigorous shaking. After the addition, the mixture was allowed to warm to room temperature and, as the heavy white precipitate separated, a further quantity of ether (30 c.c.) was added to facilitate shaking. After an hour, water (100 c.c.) was added and the mixture stored at 0° overnight. The crystalline *amide* (19 g.) was collected and recrystallised from ether from which it separated in tufts of thin long needles, m. p. 70° (Found: C, 54·0; H, 6·9; N, 4·2. $C_{16}H_{24}O_3NBr$ requires C, 53·6; H, 6·75; N, 3·9%).

11-Bromo-N-[2-(3 : 4-dimethoxyphenyl)ethyl]undecanamide (V; $n = 10$, X = Br).—11-Bromoundecanoic acid (15 g.; Ashton and Smith, *J.*, 1934, 435, 1308) and thionyl chloride (25 c.c.) were heated on a water-bath for 2·5 hours. Excess of thionyl chloride was removed under reduced pressure, benzene was added, and this in turn was removed under reduced pressure. The oily acid chloride thus obtained was, without further purification (cf. Trunel, *Compt. rend.*, 1933, **197**, 453), added in ether to 2-(3 : 4-dimethoxyphenyl)ethylamine (20·5 g.) in ether (150 c.c.) at 0° with vigorous shaking. After 0·5 hour at room temperature the product was worked up as described above, the *amide* separating from benzene–light petroleum (b. p. 40—60°) in fine white needles (20·5 g.), m. p. 88—89° (Found: C, 58·8; H, 8·0; N, 3·5. $C_{21}H_{34}O_3NBr$ requires C, 58·9; H, 8·0; N, 3·3%).

1-(5-Bromopentyl)-3 : 4-dihydro-6 : 7-dimethoxyisoquinoline Hydrochloride (cf. XVII; $n = 5$, X = Br).—6-Bromo-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]hexanamide (3·55 g.) was heated under reflux with toluene (50 c.c.) and phosphorus oxychloride (15 c.c.) for 0·5 hour. The yellow solution was allowed to cool and then diluted with light petroleum (b. p. 40—60°). The supernatant liquor was decanted from the precipitated pale yellow oil which was dissolved in water and ethanol. Excess of aqueous sodium hydroxide (2N.; 70 c.c.) was added and the liberated base was extracted with ether (2 × 30 c.c.). The ethereal layer was washed with dilute hydrochloric acid (3N.; 4 × 15 c.c.), and the acid extract was taken to dryness. The *hydrochloride* separated readily from ethanol as colourless prisms (3·03 g.), m. p. 179—181° (Found: C, 51·5; H, 6·1; N, 3·8. $C_{16}H_{23}O_2NBr,HCl$ requires C, 51·0; H, 6·2; N, 3·7%), and in dilute aqueous solution exhibited a marked blue fluorescence.

1-(10-Bromodecyl)-3 : 4-dihydro-6 : 7-dimethoxyisoquinoline Hydrochloride (cf. XVII; $n = 10$, X = Br).—11-Bromo-*N*-[2-(3 : 4-dimethoxylphenyl)ethyl]undecanamide (5 g.) was heated on the water-bath with dry toluene (50 c.c.) and phosphorus oxychloride (20 c.c.) for 40 minutes. The product was worked up as in the previous experiment and the *hydrochloride* (3·6 g.) separated from ethanol–ether in large colourless cubic prisms, m. p. 144—145° (Found, on specimen dried at 100°: C, 55·4, 55·3; H, 7·5, 7·4; N, 3·2. $C_{21}H_{32}O_2NBr,HCl,0{\cdot}5H_2O$ requires C, 55·3; H, 7·5; N, 3·1%).

3 : 4-Dihydro-6 : 7-dimethoxy-1 : 2-pentamethyleneisoquinolinium Bromide (XVIII; $n = 3$; X = Br).—1-(5-Bromopentyl)-3 : 4-dihydro-6 : 7-dimethoxyisoquinoline hydrochloride (1·18 g.) was dissolved in warm water (30 c.c.) and basified with aqueous sodium hydroxide (2N.; 20 c.c.). The precipitated oily base was extracted with ether (2 × 25 c.c.), dried (Na_2SO_4), and filtered. As the ether was removed on the steam-bath the solution became cloudy and from the residual yellow oily base some crystalline material separated out. Benzene (15 c.c.) was added and the mixture was refluxed on the water-bath for 0·5 hour. After cooling, the pale yellow needles (0·23 g.), m. p. 211—214°, which had separated were removed by filtration. The filtrate was heated for a further 0·5 hour and a further crop of crystalline material (0·13 g.) was obtained. This material was very soluble in water and gave with aqueous silver nitrate a yellow precipitate. The quaternary *bromide* separated from ethanol in hard jagged pale yellow prisms, m. p. 215—217° (Found, after air-drying: C, 49·0; H, 7·1; N, 3·3; H_2O, 13·7. $C_{16}H_{22}O_2NBr,3H_2O$ requires C, 48·7; H, 7·1; N, 3·55; H_2O, 13·7%. Found, after drying at 100°: C, 56·1; H, 6·5; N, 4·3. $C_{16}H_{22}O_2NBr$ requires C, 56·45; H, 6·5; N, 4·1%). The *picrate*, prepared by the addition of aqueous sodium picrate to a solution of the quaternary bromide, separated from ethanol in prisms, m. p. 150—151° (Found: C, 53·9; H, 5·2; N, 11·5. $C_{16}H_{22}O_2N,C_6H_2O_7N_3$ requires C, 54·1; H, 5·0; N, 11·4%). The benzene was removed from the filtrate, and from the residual gum a small amount of crystalline material slowly separated. This was dissolved in warm water, and the oily base was extracted with ether. The residue from the ethereal extract gave, when treated with dilute hydrochloric acid, a product which separated from ethanol in prisms (0·47 g.), m. p. 182°, alone or mixed with the starting material.

1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1 : 2-pentamethyleneisoquinoline Hydrobromide (cf. III; $n = 3$).—The above quaternary bromide (0·14 g.) in ethanol (1 c.c.) and concentrated hydrochloric acid (1 c.c.) was heated on the water-bath, and tin foil (0·2 g.) was added in small pieces during 0·5 hour. After an hour, the alcohol was distilled off, and the solution cooled, diluted with water, and treated with hydrogen sulphide. The tin sulphide was removed and the aqueous filtrate was taken to dryness under reduced pressure. The hydrochloride could not be induced to crystallise but the *hydrobromide* separated from ethanol–ether slowly in clusters of prisms (0·08 g.), m. p. 219—220°. Recrystallisation from ethanol

gave the pure salt in fine small needle-like prisms, m. p. 220—222° (Found: C, 55·9; H, 7·0; N, 4·5. $C_{16}H_{23}O_3N$,HBr requires C, 56·1; H, 7·1; N, 4·1%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinoline [(±)-*Salsolidine*] (IV).—3 : 4-Dihydro-6 : 7-dimethoxy-1-methylisoquinoline (4·9 g.; Spath and Polgar, *loc. cit.*) in methanol (75 c.c.) was hydrogenated at room temperature (1 atm.) in the presence of palladised strontium carbonate (3 g.; 2%). When the theoretical quantity of hydrogen had been absorbed (7 hours) the catalyst was removed by filtration and the oil obtained from the filtrate, after removal of methanol, was distilled (b. p. 138—140°/0·75 mm.; 4·1 g.). The colourless viscous liquid solidified when scratched (m. p. 43—47°), and was characterised by the *hydrobromide* which separated from ethanol in clumps of needles, m. p. 174—176° (Found: C, 49·9; H, 6·2; N, 4·8. $C_{12}H_{17}O_2N$,HBr requires C, 50·0; H, 6·4; N, 4·9%). The hydrochloride separated from ethanol as fine needles in balls, m. p. 190—191° (Found: C, 59·0; H, 7·3; N, 5·5. Calc. for $C_{12}H_{17}O_2N$,HCl: C, 59·1; H, 7·4; N, 5·7%). The picrate separated from ethanol in yellow prisms, m. p. 200—201° (Spath and Dengel, *loc. cit.*, give: hydrochloride, m. p. 196—197°, and picrate, m. p. 201—201·5°).

N-[2-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-α-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)*acetamide Hydrochloride* (cf. VI; $n = 1$).—(±)-Salsolidine (2·07 g.), α-chloro-*N*-[2-(3 : 4-dimethoxyphenyl)-ethyl]acetamide (2·57 g.), and anhydrous potassium carbonate (2 g.) in dry benzene (10 c.c.) were heated under reflux on the water-bath for 4 hours. The mixture was cooled and water and benzene were added. The benzene layer was washed with water and with dilute hydrochloric acid (3N.; 3 × 40 c.c.). The aqueous acid extract was taken to dryness under reduced presure and ethanol was twice added to the resulting gum and then distilled off. The dry viscous residue was dissolved in ethanol, and dry ether was added just to turbidity, and next morning the hard colourless prisms which had separated in clusters (4·1 g.), m. p. 65—80°, were collected and recrystallised from ethanol–ether. The *hydrochloride* of the amide was hygroscopic and the m. p. of the air-dried specimen was indefinite owing to hydration. For analysis a specimen was dried overnight at 80° and had m. p. 92° but formed a meniscus about 100° (Found: C, 61·5; H, 7·4; N, 6·1. $C_{24}H_{33}O_5N_3$,HCl requires C, 62·0; H, 7·15; N, 6·0%). The *hydrobromide* separated from ethanol–ether in clusters of small colourless prisms and an air-dried specimen had an indefinite m. p. (90—110°) (Found: C, 54·4; H, 6·8; N, 5·4; H_2O, 3·8. $C_{24}H_{33}O_5N_3$,HBr,H_2O requires C, 54·65; H, 6·7; N, 5·3; H_2O, 3·4%). When dried at 100° it gave the anhydrous form which became glassy and brittle and then had m. p. 120° (Found: C, 56·1; H, 6·6; N, 5·4. $C_{24}H_{33}O_5N_3$,HBr requires C, 56·6; H, 6·5; N, 5·5%).

N-[2-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-β-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)*propionamide Hydrochloride* (VI; $n = 1$).—(±)-Salsolidine (3·09 g.), β-chloro-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]propionamide (4·05 g.), and anhydrous potassium carbonate (2·25 g.) in dry benzene (10 c.c.) were heated together on the water-bath for 4 hours. The product was worked up as described above and the resulting gum was dissolved in ethanol to which dry ether was added to turbidity. In this case crystallisation of the hydrochloride was difficult but, after seeding, the salt separated in a woolly mass of needles (4·5 g.), m. p. 158—160°. Difficulty was experienced in removing some unchanged salsolidine hydrochloride but after several recrystallisations from ethanol the m. p. was raised to 167—168°. The seed was obtained from a previous experiment where, in order to obtain a crystalline salt, it was necessary to extract the hydrochloride solution fractionally with small portions of N-sodium hydroxide and ether into 10 fractions. The base in each fraction was then converted into the hydrochloride again and from two of these fractions the *hydrochloride* eventually separated from ethanol–ether as woolly needles in wart-like clumps, m. p. 166—167° (Found: C, 63·0; H, 7·3; N, 5·6. $C_{25}H_{34}O_5N_3$,HCl requires C, 62·7; H, 7·4; N, 5·8%). Two experiments were carried out without a solvent but the yield was not so satisfactory. Attempts to cyclise the amide with phosphorus oxychloride in boiling toluene for 0·75 hour or by the action of phosphorus pentachloride in chloroform at room temperature led to an amorphous product from which no crystalline salt could be obtained.

N-[2-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-δ-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)*valeramide Hydrochloride* (cf. VI; $n = 4$).—(±)-Salsolidine (2·07 g.), δ-bromo-*N*-[2-(3 : 4-dimethoxyphenyl)-ethyl]valeramide (3·44 g.), and anhydrous potassium carbonate (2·5 g.) in benzene (10 c.c.) were heated on the water-bath for 4 hours. The product was worked up in the usual way and the almost colourless hydrochloride gum was dissolved in ethanol and dry ether was added to turbidity. The solution was set aside at room temperature for a week, the *hydrochloride* gradually crystallising (m. p. 115—120°). Crystallisation was slow but was aided by occasional scratching but not by chilling. The hydrochloride was recrystallised from an ethanol–ether mixture and separated in colourless very small needles (4·0 g.). An air-dried specimen had m. p. 115—120° (Found: C, 57·9; H, 7·9; N, 5·2; H_2O, 9·5. $C_{27}H_{38}O_5N_3$,HCl,$3H_2O$ requires C, 57·8; H, 8·1; N, 5·0; H_2O, 9·6%. Found, after drying at 100°: C, 63·6; H, 7·8; N, 5·1. $C_{27}H_{38}O_5N_3$,HCl requires C, 63·9; H, 7·75; N, 5·5%). In two other experiments, one without solvent and the other without solvent or potassium carbonate, the results were not so satisfactory.

N-[2-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-11-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)-*undecanamide* (VI; $n = 10$).—(±)-Salsolidine (1·03 g.), 11-bromo-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]-undecanamide (2·1 g.), and potassium carbonate (1 g.) in benzene (10 c.c.) were refluxed on the water-bath for 3 hours. A further quantity of benzene was then added and the solution was made alkaline with aqueous sodium hydroxide (2N.). After the benzene extract had been dried (K_2CO_3) and the benzene removed, the resulting gum was dissolved in ether from which the *amide* separated in colourless prisms (1·25 g.), m. p. 83—85° (Found: C, 70·9; H, 8·95; N, 5·0. $C_{33}H_{50}O_5N_2$ requires C, 71·45; H, 9·1; N, 5·05%). In a subsequent experiment under similar conditions, except that the base was first extracted with dilute hydrochloric acid, the basic amide crystallised in a different *form* from ether—as woolly needles in warts, m. p. 67—70° (Found: C, 71·25; H, 8·9; N, 5·1%). This material, however, when recrystallised in the presence of a seed of the form, m. p. 83—85°, was converted into the higher-melting solid. The hydrochloride and hydrobromide of this base could not be induced to crystallise.

(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)*methane Hydrobromide* (cf. VII; $n = 1$).—*N*-[2-(3 : 4-Dimethoxyphenyl)ethyl]-α-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)acetamide hydrochloride (1·25 g.) was dissolved in water (30 c.c.) and made alkaline by the addition of excess of 2N-sodium hydroxide. The base was extracted with benzene (2 × 25 c.c.) and dried (K_2CO_3). The colourless oil thus obtained, after removal of the benzene, was dissolved in dry chloroform and cooled to −5°. Phosphorus pentachloride (1·5 g.) was then added in one lot with shaking, and the mixture, protected from moisture, was stored at 0° for 24 hours. The solution became reddish-brown as the phosphorus pentachloride gradually dissolved and a yellow solid separated. The chloroform was removed at 30° under reduced pressure and water was then added to destroy excess of pentachloride, followed by a small quantity of ethanol to dissolve the resulting oil. The solution was made alkaline with 2N-sodium hydroxide, and the base extracted with ether (2 × 50 c.c.). The ether was extracted with 3N-hydrochloric acid (3 × 30 c.c.), and the aqueous extract taken to dryness under reduced pressure. The resulting gum, after two additions of ethanol, followed by its removal on the water-bath, was dissolved in ethanol, and dry ether was added. The dihydrochloride, after seeding, separated from the solution as small yellow tablets (0·54 g.). The dihydrochloride was an unsuitable salt, being hygroscopic with an indefinite m. p. and was therefore converted into the dihydrobromide which separated from ethanol–ether in small yellow tablets, m. p. 117—119°. For analysis a sample was crystallised from a small quantity of ethanol; it had m. p. 125° when dried at 100° (Found: C, 54·3, 54·6; H, 6·2, 6·2; N, 5·5; Br, 20·6, 22·7, 22·8, 24·6, 19·4, 22·3. $C_{34}H_{36}O_4N_2,1{\cdot}5HBr$ requires C, 54·2; H, 6·0; N, 5·3; Br, 22·5%). The halogen micro-analysis was carried out on various samples but some difficulty was met in obtaining a consistent value. For air-dried material the m. p. was indefinite, 115—120° (Found: C, 52·9; H, 6·35; N, 5·4; H_2O, 3·0. $C_{34}H_{36}O_4N_2,1{\cdot}5HBr,H_2O$ requires C, 52·4; H, 6·1; N, 5·1; H_2O, 3·3%). In two subsequent experiments under the conditions described above, *i.e.*, cooling to −5° and storage at 0° for 24 hours, the product could not at first be isolated by crystallisation owing to the presence of a red gummy impurity. However, when the crude base (2·6 g.) was chromatographed on alumina with benzene, after the first two bands (bluish under ultra-violet light) had been eluted, three fractions (total, 150 c.c. of benzene) were obtained which gave the sesquihydrobromide (0·5 g.) in pale yellow tablets from alcohol and were air-dried for analysis (m. p. 115—120°) (Found: C, 49·4; H, 6·0; N, 5·0; H_2O, 9·1. $C_{34}H_{36}O_4N_2,1{\cdot}5HBr,3H_2O$ requires C, 49·2; H, 6·3; N, 4·8; H_2O, 9·2%). The seed of the hydrochloride (m. p. 70—90°) mentioned above was obtained when the reaction was carried out at room temperature as in the above experiment. Under these conditions, however, the reaction mixture became very dark and the required salt was only obtained, in low yield, from the amorphous material by fractional extraction of the hydrochloride with N-sodium hydroxide and ether.

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)-4-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)*butane Dihydrochloride* (cf. VII; $n = 4$).—*N*-[2-(3 : 4-Dimethoxyphenyl)ethyl]-δ-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)valeramide (8 g.) was dissolved in dry chloroform (40 c.c.), and phosphorus pentachloride (10 g.) was added at room temperature. Hydrogen chloride was evolved, the solution became warm, and after 1½ days the chloroform was removed and the mixture treated in the usual manner already described. The *dihydrochloride* separated readily as a crystalline powder (4·3 g.), m. p. 213—215°. Recrystallisation from ethanol afforded the pure dihydrochloride in prisms, m. p. 214—215° or 219—220° depending on the rate of heating (Found, on an air-dried specimen: C, 58·70; H, 7·3; N, 5·05; H_2O, 5·2. $C_{37}H_{46}O_4N_2,2HCl,1{\cdot}5H_2O$ requires C, 58·70; H, 7·5; N, 5·1; H_2O, 4·9. Found, on a specimen dried at 100° overnight: C, 61·7; H, 7·3; N, 5·45. $C_{37}H_{46}O_4N_2,2HCl$ requires C, 61·7; H, 7·3; N, 5·3%). The amide hydrochloride (2·72 g.) was also directly cyclised in chloroform by the same method and gave the dihydrochloride (1 g.). An attempt was made to prepare the bisquaternary methiodide by addition of methyl iodide in methanol to the bis*iso*quinoline base at room temperature. An oily quaternary salt was isolated but all attempts to crystallise it were unsuccessful. When the reactants were heated, considerable darkening of the solution occurred.

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)-5-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)*pentane Dihydrobromide* (cf. VII; $n = 5$).—(±)-Salsolidine (2·27 g.), 6-bromo-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]hexanamide (3·55 g.), and potassium carbonate (anhyd.; 3 g.) were heated under reflux in benzene (15 c.c.) for 4 hours. Water and aqueous sodium hydroxide (2N.; 10 c.c.) were added and the base was extracted with benzene (2 × 25 c.c.) which was washed with water and then hydrochloric acid (3N.). Owing to the sparing solubility of the amide hydrochloride three layers were formed. The two bottom layers were run off and, on warming, a homogeneous aqueous solution was obtained. The benzene solution was extracted again with acid, and the aqueous fractions were taken to dryness. All attempts to obtain the crystalline amide hydrochloride were unsuccessful. The base amide (5·05 g.) was obtained by basification of the aqueous solution of the salt, followed by extraction with benzene (3 × 50 c.c.), as a light brown oil and was cyclised without further purification by dissolving it in dry chloroform (40 c.c.), cooling the solution to −5°, and adding phosphorus pentachloride (5 g.). The reaction mixture was left at room temperature overnight and was worked up in the manner described above. The hydrochloride of the pentane derivative could not be induced to crystallise but the *dihydrobromide* gradually separated overnight from ethanol–ether in yellow round nodules (4·8 g.), m. p. 198—200°. The pure salt separated from methanol–ether in small pale yellow prisms, m. p. 205—207°. A sample was air-dried for analysis (Found: C, 50·5; H, 6·7; N, 4·3; H_2O, 5·5. $C_{38}H_{50}O_4N_2,2HBr,2H_2O$ requires C, 50·6; H, 6·7; N, 4·2; H_2O, 5·4%).

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)-10-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)*decane Dihydrogen Dioxalate* (cf. VII; $n = 10$).—The decanamide (11 g.) in chloroform (100 c.c.) was treated at 0° with phosphorus pentachloride (15 g.) and kept at room temperature overnight. The product was worked up in the manner already described, to give a gummy hydrochloride which, however, could not be induced to crystallise. Attempts to obtain the crystalline hydrobromide, hydriodide, picrate, thiocyanate, and platinum salts, and base were equally unsuccessful. The product,

however, appeared to be homogeneous since, on fractional extraction of the hydrobromide solution with 2N-sodium hydroxide (3-c.c. portions) and ether into 7 fractions, the bulk of the material was found in the 4th and 5th fractions. Eventually a *dihydrogen dioxalate* was obtained which separated from ethanol after several days in a jelly-like form but was microcrystalline under polarised light. When dried in a vacuum-desiccator over concentrated sulphuric acid it collapsed and formed a hard yellow brittle mass which softened at 95° and had m. p. 105—108° (Found: C, 60·3, 60·3; H, 7·0, 7·3. $C_{22}H_{41}O_4N_3,2H_2C_2O_4,1H_2O$ requires C, 60·5; H, 7·4%). A portion (1·85 g.) of the non-crystalline dihydrobromide obtained from the 5th fraction, in water (50 c.c.) and hydrochloric acid (3N.; 10 c.c.), in the presence of Adams's catalyst, slowly absorbed hydrogen (86 c.c. at 20°/755 mm.) overnight. No crystalline salt could be obtained, however, from this reduction, even after chromatography on alumina which, however, indicated that the product was essentially homogeneous, and this material was used in the biological test, neutralised to pH 7 by dilute hydrochloric acid.

1-*Cyanomethyl*-3 : 4-*dihydro*-6 : 7-*dimethoxy*isoquinoline.—α-Cyano-*N*-[2-(3 : 4-dimethoxyphenyl)-ethyl]acetamide (18 g.; Child and Pyman, *loc. cit.*, 1931) was dissolved in hot toluene (200 c.c.) and to the boiling solution phosphoric oxide (60 g.) was added in two portions at intervals of 30 minutes. After the mixture had been heated under reflux for a total of 2·5 hours the hot toluene layer was decanted and, on cooling, some unchanged amide (1·1 g.) crystallised. The solid residue was carefully decomposed by the addition of water, and the yellow-brown aqueous solution was extracted with ether to remove the last traces of toluene. The acid aqueous extract was made alkaline with aqueous sodium hydroxide (50%; 100 c.c.) at 0° and the yellow crystalline precipitate was collected and recrystallised once from ethanol (450 c.c.) from which it separated in yellow prisms (9·15 g.), m. p. 170° (Child and Pyman, *loc. cit.*, 1931, give m. p. 173°).

Ethyl 3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylacetate* (X).—The cyano-*iso*quinoline (6·9 g.) was dissolved, with warming, in absolute ethyl alcohol (150 c.c.), and dry hydrogen chloride was passed into the solution for 2 hours at 0°. The mixture was stored at 0° overnight and then heated under reflux for 2 hours. The ammonium chloride was removed by filtration and the alcoholic filtrate was concentrated to 25 c.c. Water (100 c.c.) was added and the solution was made alkaline by the addition of aqueous sodium hydroxide (2N.). The yellow oil, which was extracted with ether (3 × 50 c.c.) and dried (K_2CO_3), afforded after removal of the ether the ester (7·2 g.) in crystalline form when left under light petroleum (b. p. 40—60°) overnight. The ester was recrystallised from light petroleum (250 c.c.) from which it separated in hard yellow prisms in clusters in two *forms*, yellow needle-like prisms in clumps, m. p. 80—82° (Found: C, 64·9; H, 6·7; N, 5·6. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·8; N, 5·1%), and cubic prisms m. p. 86—87° (Found: C, 65·1; H, 6·4; N, 4·9%). Battersby and Openshaw (*Experientia, loc. cit.*) give m. p. 85·5—86·5°. The *picrate* separated from ethanol, in which it was sparingly soluble, in yellow needles, m. p. 170—171° (Found: C, 49·9; H, 4·2; N, 11·3. $C_{15}H_{19}O_4N,C_6H_3O_7N_3$ requires C, 49·8; H, 4·4; N, 11·1%). The *hydrobromide* separated from ethanol–ether as large yellow prisms. It sintered at 155° and had m. p. 160° (decomp.) (Found, in air-dried specimen: C, 49·4; H, 5·6; N, 3·8; H_2O, 3·0. $C_{15}H_{19}O_4N,HBr,0{\cdot}5H_2O$ requires C, 49·1; H, 5·75; N, 3·8; H_2O, 2·45%).

3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinoline*.—Ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*-quinolylacetate (0·35 g.) was refluxed on the water-bath with alcoholic potassium hydroxide (5%; 10 c.c.) for 0·5 hour. Water (10 c.c.) was added and the alcohol was allowed to distil off (0·5 hour). The base was extracted with benzene, washed with water, and dried (K_2CO_3). The benzene extract was concentrated and light petroleum was added. The large prisms, m. p. 102—103°, that separated were recrystallised from benzene–light petroleum, to give the dihydro*iso*quinoline (0·25 g.) in prisms, m. p. and mixed m. p. with an authentic specimen, 103—104° (Found: N, 6·4. Calc. for $C_{12}H_{15}O_2N$: N, 6·8%); the picrate had m. p. 209—211°. Spath and Polgar (*loc. cit.*) give m. p. 106—107°, and picrate m. p. 210—212°.

Ethyl α-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-β-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*-iso*quinolino*)*propionate Dihydrobromide* (cf. XI).—(±)-Salsolidine (1·03 g.) and ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylacetate (1·38 g.) were dissolved in aqueous acetic acid (50%; 10 c.c.) with warming. Formalin (40%; 0·5 c.c.) was added and the solution left at room temperature for 20 hours. Water was added and the solution, after extraction with ether, was made alkaline with excess of sodium hydroxide solution (2N.), and the bases were extracted with ether. The viscous yellow oil, obtained after removal of the ether, triturated with a little alcohol and cooled to 0°, gave a yellow granular deposit (0·5 g.) which separated from benzene in large yellow rectangular prisms, m. p. 156—180°. After three recrystallisations from benzene, base (C), m. p. 180—181°, was obtained which gave no depression of the m. p. on admixture with *ethyl* α-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*acrylate* (see below) (Found: C, 66·8; H, 7·0; N, 5·0. $C_{16}H_{19}O_4N$ requires C, 66·4; H, 6·6; N, 4·8%). From the benzene mother-liquors a second compound was isolated in small yield and after several recrystallisations from benzene gave colourless prisms, base B; the m. p. and mixed m. p. with ethyl αα′-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-isoquinolyl)glutarate was 183—185°. A mixed m. p. with base (C) gave a depression to 165—175°. When this material was treated with hot aqueous alcoholic potassium hydroxide for 0·5 hour on the water-bath (see below) a new base (D) was obtained which separated from alcohol in fine needles, m. p. and mixed m. p. with 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane 159—161°. To the alcoholic mother-liquor after removal of bases (B) and (C) was added hydrobromic acid (N.; 6 c.c.), the solution was taken to dryness, and the residue was dissolved in ethanol from which the *dihydrobromide* separated slowly on the addition of ether as yellow prisms (0·55 g.), m. p. 163—170° (decomp.). After three recrystallisations from ethanol the pure salt was obtained in clumps of prisms, m. p. 174—175° (decomp.) (melted to a red liquid with evolution of small bubbles), and gave a depression when admixed with (±)-salsolidine hydrobromide to 170—173°; when air-dried a specimen, had m. p. 172—174° (decomp.) (Found: C, 50·2; H, 6·4; N, 4·4; H_2O, 0·8. $C_{18}H_{24}O_4N_2,2HBr,0{\cdot}5H_2O$ requires C, 50·3; H, 6·2; N, 4·2; H_2O, 1·3%). The dihydrochloride separated from ethanol–ether in

clumps of prisms, m. p. 173—175° (decomp.). The dihydrobromide (0·41 g.) in dilute hydrochloric acid was reduced in the presence of Adams's catalyst at atmospheric pressure and slowly absorbed 20 c.c. of hydrogen (theoretical, 15 c.c.) overnight. A crystalline hydrobromide could not be obtained from the reduction mixture.

1 : 2 : 3 : 4-*Tetrahydro*-2-3′-*indolylmethyl*-6 : 7-*dimethoxy*-1-*methylisoquinoline* (XII).—(±)-Salsolidine (1·03 g.), indole (0·58 g.), and formaldehyde (40%; 0·5 c.c.) in aqueous acetic acid (50%; 10 c.c.) were set aside at room temperature for 2 days. The solution was made alkaline with sodium hydroxide solution (2N.), and the basic material was extracted with ether and dried (K_2CO_3). After removal of the ether the resulting gum was dissolved in ethanol–ethyl acetate, and light petroleum was added with scratching. A crystalline solid (0·84 g.) slowly separated, having m. p. 125—130° which, after recrystallisation from benzene–light petroleum (b. p. 40—60°) and then twice from *iso*propyl alcohol, gave the pure *base* in clusters of prisms (0·35 g.), m. p. 135—137° or 139—141° depending on the rate of heating (Found: C, 74·8; H, 7·3; N, 8·4. $C_{21}H_{24}O_2N_2$ requires C, 75·2; H, 6·9; N, 8·35%). A solution of the base in dilute hydrochloric acid gradually became violet.

Ethyl α-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)*acrylate* (XV).—Ethyl (3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)acetate (1·1 g.; 1 mol.) and aqueous formaldehyde (0·6 c.c.; 20%; 1 mol.) in aqueous acetic acid (10 c.c.; 50%) were kept at room temperature for 19 hours. The solution was made alkaline by the addition of sodium hydroxide solution (2N.), and the basic material was extracted with chloroform (2 × 40 c.c.), washed with water, and dried (K_2CO_3). After removal of the chloroform, the residue was dissolved in a small volume of benzene and diluted with twice its volume of dry ether. The hard yellow cubic prisms (0·81 g.), m. p. 175—179°, were collected and recrystallised from benzene and then had m. p. 179—181° alone or mixed with base C obtained in the Mannich reaction between the ester (X) and (±)-salsolidine as described above.

Ethyl αα′-*Bis*-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)*glutarate* (XIII; R = CO_2Et, n = 1).—Ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylacetate (1·1 g.; 2 mols.) and aqueous formaldehyde (0·3 c.c.; 20%; 1 mol.) in aqueous acetic acid (10 c.c.; 50%) were kept at room temperature for 19 hours. The solution was made alkaline with excess of sodium hydroxide solution (2N.), and the basic material was extracted with chloroform (2 × 40 c.c.), washed with water, and dried (K_2CO_3). The *base*, after removal of the chloroform, when treated with benzene and ether gave colourless prisms (0·54 g.), m. p. 178—182°, which separated from benzene in hard colourless prisms, m. p. 182—183° (Found: C, 65·5; H, 6·4; N, 4·7. $C_{31}H_{38}O_4N_2$ requires C, 65·7; H, 6·7; N, 4·9%). This material gave, as described below, on alkaline hydrolysis 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane, m. p. 162—163°. From the mother-liquor a microcrystalline solid (0·1 g.), m. p. 150—160° gradually separated out at 0° and, after two recrystallisations from benzene–ether, the second, isomeric *base* had m. p. 157—161° (Found: C, 65·4; H, 6·9. $C_{31}H_{38}O_4N_2$ requires C, 65·7; H, 6·7%). This isomer also gave, when treated with aqueous alcoholic potassium hydroxide (5%), 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane, m. p. and mixed m. p. 158—159°.

1 : 4-*Bis*-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)*butane* (XIII; n = 2; R = H).—*NN′*-[2-(3 : 4-Dimethoxyphenyl)ethyl]adipdiamide (3 g.) was dissolved in dry chloroform (25 c.c.), and phosphorus pentachloride (6 g.) was added in one lot with shaking. Hydrogen chloride was evolved and the reaction mixture cooled and then set aside at room temperature for 12 hours, whereupon a yellow granular deposit separated. The chloroform was removed under reduced pressure, the residue was dissolved in ethanol, and the solution made alkaline with sodium hydroxide solution. After dilution of this solution with water the felted needles that separated were collected and crystallised from ethyl acetate as needles (0·8 g.), m. p. 170—171° (Child and Pyman, *loc. cit.*, 1929, give m. p. 172—173°).

1 : 3-*Bis*-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)*propane* (XIII; n = 1; R = H).—(*a*) To a solution of *NN′*-[2-(3 : 4-dimethoxyphenyl)ethyl]glutardiamide (5 g.) in boiling dry toluene (100 c.c.) was added phosphoric oxide (15 g.) in one lot with constant shaking, and after an hour a further portion of phosphoric oxide (5 g.) was added. After the mixture had been refluxed for a total of 2·75 hours the toluene layer was decanted whilst hot and the residual cake, after cooling, was cautiously decomposed with water. The toluene layer was separated and the aqueous layer was extracted once with ether and then made strongly alkaline with aqueous sodium hydroxide (50%). The yellow oil which separated gave, when scratched and cooled to 0°, a partly solid material which was collected, washed with water, and dissolved in a minimum quantity of ethanol. The *base* separated in a mass of felted needles (1·6 g.), m. p. 159—161° (Found: C, 70·8; H, 7·2; N, 6·5. $C_{29}H_{36}O_4N_2$ requires C, 71·05; H, 7·2; N, 6·6%). The *dihydrobromide* separated from ethanol as pale yellow prisms which, when air-dried, softened at 214° with m. p. 216—218° (Found: C, 50·0; H, 5·4; H_2O, 3·0. $C_{29}H_{36}O_4N_2.2HBr,1H_2O$ requires C, 49·8; H, 5·7; H_2O, 3·0%). When dried at 130° it became anhydrous (Found: N, 4·9. $C_{29}H_{36}O_4N_2.2HBr$ requires N, 4·8%). The dihydrochloride separated from ethanol in thick rod-like prisms, m. p. 195—205° (decomp.). The alcoholic mother-liquors were combined, the ethanol was removed, and the residue taken up in benzene and cooled at 0°. The white felted needles (0·36 g.) which separated proved to be unchanged starting material, m. p. and mixed m. p. 128—130°. The filtrate was concentrated and on protracted storage a crystalline solid formed in the residual gum. It was removed and crystallised from benzene from which it separated in transparent prisms (0·9 g.), m. p. 135° (Found: C, 68·25; H, 7·0; N, 6·45. $C_{28}H_{32}O_5N_2$ requires C, 68·15; H, 7·3; N, 6·4%). This base was considered to be γ-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*isoquinolyl*)-*N*-[2-(3 : 4-*dimethoxyphenyl*)*ethyl*]*butyramide* and it gave a *monohydriodide* which separated from methanol as yellow needles, m. p. 133—135° (Found: C, 52·9; H, 5·8; N, 5·0. $C_{28}H_{33}O_5N_2I$ requires C, 52·8; H, 5·85; N, 4·9%). When the basic amide (79 mg.) was dissolved in boiling dry toluene (5 c.c.) and treated with phosphoric oxide (0·5 g.) and heated at 120° (oil-bath) for 2 hours it gave, after being worked up as described above, 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane, which separated from benzene and then from ethanol as a mass of fine colourless needles (20 mg.), m. p. and mixed m. p. 161—162°.

(*b*) Ethyl *aa'*-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)glutarate (0·35 g.) (XIII; $n = 1$, R = CO_2Et) was refluxed on the water-bath with alcoholic potassium hydroxide (10 c.c.; 5%) for 0·5 hour. The white solid which separated dissolved on addition of water (2 c.c.). After a further 0·5 hour's heating more water (*ca.* 10 c.c.) was added and most of the alcohol was allowed to distil off. On cooling, the yellow oil, which crystallised when scratched to fine needles, was collected and crystallised from ethanol as a mass of fine felted needles (0·2 g.), m. p. 162—163° alone or mixed m. p. with the bis*iso*quinolylpropane obtained in (*a*).

1 : 3-*Bis*-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*propane Dihydrobromides* (cf. II; $n = 3$).—To a boiling solution of 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (0·56 g.) in ethanol (2·5 c.c.) and concentrated hydrochloric acid (2·5 c.c.), tin (1·5 g.) was added and the mixture was refluxed for 4 hours with a further addition of acid (1 c.c.) after 1 hour. The alcohol was distilled off, and the solution was diluted with water and treated with hydrogen sulphide. The sulphide was removed by filtration and washed with warm water. The filtrate was made alkaline with aqueous sodium hydroxide (50%), and the basic material extracted with ether. After removal of the ether the residue was dissolved in a small quantity of alcohol but no crystalline base could be obtained. A small amount of amorphous material was removed and the filtrate treated with excess of hydrobromic acid (2N.) and taken to dryness. The *dihydrobromide* A separated from ethanol readily in needle-like prisms (0·21 g.), m. p. 268—270°, and then from methanol as colourless needles, m. p. 270—272° with shrinking at 267° (Found, in material dried at 130°: C, 51·4; H, 6·4; N, 5·0. $C_{25}H_{34}O_4N_2.2HBr$ requires C, 51·0; H, 6·2; N, 4·8%). To the alcoholic mother-liquor ether was added and after several days a second isomer separated in round clumps (hemispherical) (0·13 g.), m. p. 240—243°, together with some feathery needles of the first isomer (m. p. 265°). The *dihydrobromide* B separated from methanol as fine needles in bundles, m. p. 237—239° (Found, on air-dried sample: C, 50·5; H, 6·1; H_2O, 1·6. $C_{25}H_{34}O_4N_2.2HBr,0{\cdot}5H_2O$ requires C, 50·3; H, 6·2; H_2O, 1·5%).

Bis-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)*methane* (XVI).—(±)-Salsolidine (1·03 g.) and aqueous formaldehyde (0·25 c.c.; 40%) were condensed in aqueous acetic acid (20 c.c.; 25%) at 100° for an hour. The solution was made alkaline and the base was extracted with ether and dried (K_2CO_3). The clear colourless oil, obtained by removal of the ether, was scratched in benzene–light petroleum (b.p. 40—60°), and cooling to 0° gave a solid. The *base* separated from benzene–light petroleum (b. p. 40—60°) as hard colourless prisms (0·3 g.), m. p. 105—107° (Found: C, 70·1; H, 8·2; N, 6·6. $C_{25}H_{34}O_4N_2$ requires C, 70·4; H, 8·0; N, 6·6%).

(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*methane Hydrobromide* (cf. VIII; $n = 1$).—(3 : 4-Dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)methane hydrobromide (0·57 g.) was dissolved in water (30 c.c.) and dilute hydrochloric acid (3N.; 5 c.c.) and hydrogenated at 1 atmosphere and room temperature in the presence of Adams's catalyst. The absorption of hydrogen was rapid at first but soon became slower and after overnight shaking 36 c.c. were absorbed (temp. = 18°). The catalyst was removed by filtration and the filtrate taken to dryness under reduced pressure. An excess of hydrobromic acid (2N.) was added; the *sesquihydrobromide* separated from ethanol–ether as a micro-crystalline powder (0·3 g.). The salt crystallised from ethanol in small well-defined colourless prisms which after drying at 100° had m. p. 130—132° with the meniscus forming at 140° (Found, on air-dried sample: C, 49·3; H, 6·5; N, 5·3; H_2O, 8·8; Br, 20·3. $C_{24}H_{32}O_4N_2.1{\cdot}5HBr,3H_2O$ requires C, 49·0; H, 6·8; N, 4·8; H_2O, 9·2; Br, 20·4%). No crystalline material could be obtained from the mother-liquors.

1-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)-4-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*butane Dihydrogen Dioxalate* (cf. VIII; $n = 4$).—The corresponding propane dihydro*iso*quinoline dihydrochloride (0·52 g.) in water (30 c.c.) and dilute hydrochloric acid (3N.; 5 c.c.) was hydrogenated in the presence of Adams's catalyst (0·1 g.). After overnight shaking the catalyst was removed and the filtrate, which was no longer fluorescent under ultra-violet light, was taken to dryness. Attempts to crystallise the dihydrochloride were unsuccessful. The base, however, obtained by addition of aqueous sodium hydroxide to the salt solution and extraction with ether (2 × 50 c.c.), gave when treated with oxalic acid (anhyd.; 0·2 g.) a *dihydrogen dioxalate* as an amorphous powder (0·4 g.), m. p. 125—120° with the meniscus forming at 160°. The salt after several crystallisations from ethanol, from which it separated very slowly during several days in small nodules of woolly needles, was obtained pure (0·26 g.) with m. p. (of air-dried specimen) 90—130° (Found: C, 54·75; H, 6·9; N, 4·5; H_2O, 6·4. $C_{27}H_{38}O_4N_2.2H_2C_2O_4.2{\cdot}5H_2O$ requires C, 54·8; H, 7·0; N, 4·1; H_2O, 6·6%). A sample dried at 110° had m. p. 140—145° (Found: C, 59·2; H, 7·3; N, 4·8. $C_{27}H_{38}O_4N_2.2H_2C_2O_4$ requires C, 58·7; H, 6·8; N, 4·4%).

1-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)-5-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*pentane Dihydrogen Dioxalates* (cf. VIII; $n = 5$).—The corresponding pentane dihydro*iso*quinoline dihydrobromide (1·2 g.) in water (60 c.c.) and dilute hydrochloric acid (3N.; 10 c.c.) was hydrogenated in the presence of Adams's catalyst (0·06 g.). Absorption of hydrogen was rapid at first and the theoretical quantity was absorbed after 4 hours. After the catalyst had been removed, the filtrate was made alkaline with aqueous sodium hydroxide (2N.; 30 c.c.), and the base extracted with ether (2 × 50 c.c.). After removal of the ether, the base was dissolved in ethanol (30 c.c.), and oxalic acid (0·55 g.) in ethanol (10 c.c.) was added. A white crystalline material (0·72 g.), m. p. 184—189°, slowly separated overnight at 0°. The *dihydrogen dioxalate* A, which was sparingly soluble in ethanol, separated from methanol in colourless cubic prisms, m. p. 192—194° (Found: C, 59·5; H, 6·9; N, 4·4. $C_{28}H_{40}O_4N_2.2H_2C_2O_4$ requires C, 59·2; H, 6·8; N, 4·3%). From the mother-liquor on concentration a second racemate was obtained, on long storage, as large prisms (0·33 g.), m. p. 153—155°. This *dihydrogen dioxalate* B separated from methanol–ether in small colourless prisms, m. p. 150—152° (Found, in air-dried specimen: C, 56·9; H, 6·85; N, 4·3; H_2O, 4·6. $C_{28}H_{40}O_4N_2.2H_2C_2O_4.1{\cdot}5H_2O$ requires C, 57·0; H, 7·0; N, 4·1; H_2O, 4·0%).

3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*piperidinomethylisoquinoline Dihydrochloride* (cf. XVII; X = piperidino).—To 1-chloromethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline hydrochloride (3·0 g.) piperidine (20 c.c.) was added with vigorous shaking and warming on the water-bath for 10 minutes. The mixture was then heated at 95° for 2 hours. Water and chloroform were then added together with excess of 2N-sodium hydroxide, and the chloroform layer separated. After the chloroform and excess of piperidine had been removed under reduced pressure, the red gummy residue was treated with excess of 2N-hydrochloric acid, and the solution was taken to dryness. The *dihydrochloride* (1·78 g.) sintered at 165°, had m. p. 180° (decomp.), separated from ethanol in flat square yellow prisms and after two recrystallisations sintered at 150° and melted at 195—198° (decomp.) (Found : C, 56·45; H, 7·2; N, 7·6. $C_{17}H_{24}O_2N_2,2HCl$ requires C, 56·5; H, 7·25; N, 7·75%).

***Attempted Condensation between* 1-*Chloromethyl*-3 : 4-*dihydro*-6 : 7-*dimethoxy*isoquinoline *and* (±)-*Salsolidine*.**—(±)-Salsolidine (2·07 g.; 2 mols.) was added to an ethereal solution of the chloro-base [derived from the hydrochloride (1·37 g.; 1 mol.) by treatment with sodium carbonate and ether] and after the ether had been distilled off benzene (15 c.c.) was added and the solution was heated on the water-bath for 2 hours. Crystals separated in the first few minutes and these were collected (0·84 g.) and recrystallised from ethanol, to give (±)-salsolidine hydrochloride, m. p. 188—190°. No crystalline salt could be isolated from the mother-liquor (green), and the crude base when chromatographed on alumina in benzene showed at least 9 bands. No crystalline material could be isolated from any of these bands.

Ethyl* 1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolinoacetate Hydrobromide (cf. XIX; n = 1).—(±)-Salsolidine (2·07 g.), ethyl chloroacetate (1·22 g.), and anhydrous potassium carbonate (1·5 g.) were refluxed in benzene (5 c.c.) for 3 hours. Water was added and the base was extracted with benzene and dried (K_2CO_3). Distillation of the residue gave a pale yellow viscous oil (2·06 g.) (b. p. 180°/0·5 mm.), the *hydrobromide* of which separated from ethanol in prisms, m. p. 186—188° (decomp.) (Found : C, 51·3; H, 6·3; N, 3·7. $C_{14}H_{22}O_4N,HBr$ requires C, 51·3; H, 6·5; N, 3·7%).

Ethyl* γ-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methylisoquinolino*)*butyrate Hydrobromide (XIX; n = 3).—This was prepared in a similar way, from (±)-salsolidine (2·07 g.), ethyl γ-bromobutyrate (1·95 g.), and potassium carbonate (1·5 g.) in benzene (15 c.c.). The *hydrobromide* (1·65 g.), m. p. 164—165°, separated from ethanol in fine white needles (Found : C, 53·7; H, 7·3; N, 3·5. $C_{18}H_{27}O_4N,HBr$ requires C, 53·75; H, 7·0; N, 3·5%). An attempt was made to condense the base with 3 : 4-dimethoxyphenylethylamine at 180° and at 200—210° for 7 hours. Under the former conditions half of the propionate was recovered unchanged and under the latter the reaction mixture became rather dark and tarry. An attempt was made to cyclise the crude amide, which could not be crystallised, but no useful product resulted.

The author thanks Dr. H. King, C.B.E., F.R.S., for his encouragement and for his interest in this work, Dr. J. D. Fulton for the biological results, and Glaxo Laboratories for a gift of 3 : 4-dimethoxybenzyl cyanide.

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[*Received, August 21st*, 1951.]

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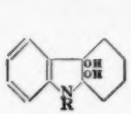
767. *Oxindoles formerly regarded as ψ-Indoxyls.*

By R. F. MOORE and S. G. P. PLANT.

*cyclo*Pentane*spiro*oxindole, *cyclo*hexane*spiro*oxindole, and several derivatives of the latter have been synthesised from the appropriate phenylhydrazides of *cyclo*pentane- or *cyclo*hexane-carboxylic acid. Some of these products had hitherto been regarded as ψ-indoxyls. The position of the substituent in the nitration product of *cyclo*hexane*spiro*oxindole has been established, and the course of the Friedel–Crafts reaction in the 3 : 3-disubstituted oxindole group has been investigated.

IT was observed by Perkin and Plant (*J.*, 1923, **123**, 676) that 9-acylhexahydro-10 : 11-dihydroxycarbazoles (I; R = acyl), from the action of nitric acid on the corresponding acyltetrahydrocarbazoles (II; R = acyl) in acetic acid, undergo a pinacolinic change on being heated alone or in acetic anhydride to give compounds which can readily be deacylated. Of the two alternative structures for the product, $C_{13}H_{13}ON$, the ψ-indoxyl formulation (III) seemed the more probable at the time, and this was later supported by observations which are referred to below. It has more recently been shown by Plant and Robinson (*Nature*, 1950, **165**, 36) that this view is untenable and that the substance must be *cyclo*pentane*spiro*oxindole (IV). Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 614) independently reached the same conclusion, and Patrick and Witkop (*ibid.*, p. 633) indirectly confirmed the oxindole formulation by showing that nitration of the material obtained by condensing 1-methyloxindole with tetramethylene dibromide gave a compound (V; R = Me) identical with the substance prepared by Perkin

and Plant by nitration of the compound $C_{12}H_{13}ON$ and subsequent methylation. The position of the nitro-group is not hereby established, but it follows from the fact that the unmethylated substance (V; R = H) has also been obtained (Massey and Plant, *J.*, 1931, 2218) by applying the above sequence of reactions to 9-acetyl-6-nitrotetrahydrocarbazole (VI).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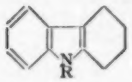
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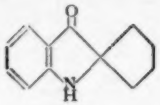
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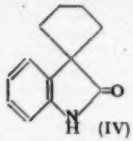
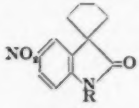

(IV)

It seemed desirable to add the confirmation of a direct synthesis of (IV), and this has now been done by using a method of preparing oxindoles developed by Brunner (*Monatsh.*, 1896, **17**, 479; 1897, **18**, 95), *viz.*, the elimination of ammonia from phenylhydrazides of the type, $C_6H_5{\cdot}NR{\cdot}NH{\cdot}CO{\cdot}CHR'R''$, by heating with quicklime. For the present purpose, the phenylhydrazide of *cyclo*pentanecarboxylic acid was prepared.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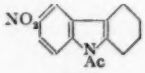
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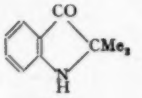
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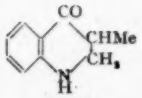
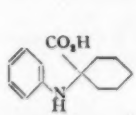

(VIII)

Bucherer and Grolée (*Ber.*, 1906, **39**, 986) heated the anilino*iso*butyric acid, m. p. 185°, with a mixture of sodium ethoxide and potassium hydroxide and isolated a product which they thought to be 2 : 2-dimethyl-ψ-indoxyl (VII) or 1 : 2 : 3 : 4-tetrahydro-4-keto-3-methylquinoline (VIII). Betts, Muspratt, and Plant (*J.*, 1927, 1310), using similar conditions with 1-anilino*cyclo*hexane-1-carboxylic acid (IX), obtained a substance regarded as *cyclo*hexane-*spiro*-ψ-indoxyl (X), and the close resemblance of the latter to the *spiro*-compound $C_{12}H_{13}ON$ obtained from tetrahydrocarbazole provided strong mutual support for the formulations proposed. By an extension of the synthetical method and reactions with the products, Betts and Plant (*J.*, 1928, 2070) have prepared other substances formulated as derivatives of (X). It is now evident (Plant and Robinson, *loc. cit.*) that the isomeric oxindole structure almost certainly must also be attributed to these compounds, and Mr. L. J. Goldsworthy has shown that the substance described by Bucherer and Grolée is identical with 3 : 3-dimethyloxindole (XI) obtained from *iso*butyrophenylhydrazide (see Plant, Robinson, and Tomlinson, *Nature*, 1950, **165**, 928).

The application of Brunner's reaction to the phenylhydrazide and the *o*- and *p*-tolylhydrazides of *cyclo*hexanecarboxylic acid has now given *cyclo*hexane*spiro*oxindole (XII) and derivatives identical with the substances referred to above, and afforded synthetical confirmation of the more recent structural views.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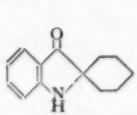
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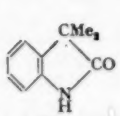
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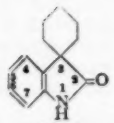
(XII)

Like the *cyclo*pentane analogue, the compound (XII) very readily gives a nitro-derivative (*J.*, 1927, 1310), but the position of the substituent has not hitherto been rigidly established. In an attempt to do this, *cyclo*hexane*spiro*-5-methoxyoxindole was synthesised from the *p*-methoxyphenylhydrazide of *cyclo*hexanecarboxylic acid, and the nitro-compound reduced to the amine, but the conversion of the latter into the corresponding phenol proved to be difficult. The amine was accordingly converted by a Sandmeyer reaction into a chloro-compound identical with *cyclo*hexane*spiro*-5-chloro-oxindole prepared from the appropriate *p*-chlorophenylhydrazide.

The possibility of applying the Friedel–Crafts reaction to the 3 : 3-disubstituted oxindoles has been studied. The action of acetyl chloride and aluminium chloride on 3 : 3-dimethyl-

oxindole in carbon disulphide gave 5-acetyl-3 : 3-dimethyloxindole, the nature of which was confirmed by the preparation of a *N*-acetyl derivative and an oxime. Its constitution followed from the fact that the oxime, by a Beckmann rearrangement, gave an acetamido-compound which on hydrolysis yielded 5-amino-3 : 3-dimethyloxindole, already prepared by an unambiguous route (Brunner, *Monatsh.*, 1931, **58**, 369). The 5-acetyl compound was added to molten potassium hydroxide, and acidification of the mixture gave 3 : 3-dimethyl-oxindole-5-carboxylic acid.

Similar treatment of the compound (XII) gave *cyclo*hexane*spiro*-5-acetyloxindole, the structure of which was also proved by rearrangement of its oxime and hydrolysis of the product to *cyclo*hexane*spiro*-5-amino-oxindole. In fact this is a more convenient way of obtaining the amine than by reduction of the nitro-compound.

Experimental.

Synthesis of cyclo*Pentane*spiro*oxindole*.—Phenylhydrazine (72 g., 2 mols.) in dry ether (150 c.c.) was slowly added to *cyclo*pentanecarboxyl chloride (44 g.) in dry ether (100 c.c.) with mechanical stirring under a reflux condenser, and cooling in ice-water. After the mixture had been stirred for a further 20 minutes, the ether was removed by evaporation, the residue shaken with water, and the insoluble material crystallised from aqueous ethanol, from which the *phenylhydrazide* of *cyclo*pentanecarboxylic acid separated in colourless needles (yield, 70%), m. p. 111° (Found : C, 71·1; H, 7·8. $C_{12}H_{14}ON_2$ requires C, 70·6; H, 7·8%). A mixture of the phenylhydrazide (15 g.) and powdered quicklime (45 g.) was heated for 3 hours at 230—250°, and, when cold, it was powdered and cautiously treated with hydrochloric acid (300 c.c. of 20%), and the whole refluxed for an hour. The insoluble product was extracted with ether, the extract dried ($CaCl_2$), the solvent removed, and the residue distilled under reduced pressure. Crystallisation of the distillate from light petroleum gave nearly pure *cyclo*pentane-*spiro*oxindole (6 g.), m. p. 105—110°. Further purification was effected by refluxing the product with acetic anhydride (30 c.c.) for an hour, and pouring the cold solution into an excess of water. The precipitated *cyclo*pentane*spiro*-1-acetyloxindole separated from ethanol in long, colourless prisms (6 g.), m. p. 104°, and was hydrolysed by boiling for ½ hour with aqueous-ethanolic potassium hydroxide; the resulting *cyclo*pentane*spiro*oxindole then crystallised from light petroleum in colourless plates (4·5 g.), m. p. 113°. This substance and its acetyl derivative were shown to be identical (mixed m. p.) with the substances obtained by Perkin and Plant (*loc. cit.*) by heating 9-acetyl-10 : 11-dihydroxyhexahydrocarbazole either alone or with acetic anhydride.

Synthesis of cyclo*Hexane*spiro*oxindole and Derivatives*.—By using steps similar to those described above, the phenylhydrazide of *cyclo*hexanecarboxylic acid, m. p. 164° (compare Rupe and Metz, *Ber.*, 1903, **36**, 1092), was prepared and converted into *cyclo*hexane*spiro*oxindole (yield, 35%), colourless prisms (from light petroleum), m. p. 124°, and *cyclo*hexane*spiro*-1-acetyloxindole, colourless prisms (from methanol), m. p. 105°. The last two were shown by mixed m. p. to be identical with the substances obtained by Betts, Muspratt, and Plant (*loc. cit.*) from 1-anilino*cyclo*hexane-1-carboxylic acid.

In a similar manner the *o-tolylhydrazide*, colourless needles (from aqueous ethanol), m. p. 167° (Found : C, 72·7; H, 8·7. $C_{14}H_{20}ON_2$ requires C, 72·4; H, 8·6%), and *p-tolylhydrazide*, colourless needles (from aqueous ethanol), m. p. 156° (Found : C, 72·6; H, 8·6%), of *cyclo*hexanecarboxylic acid were obtained. From them, *cyclo*hexane*spiro*-7-methyloxindole, colourless prisms (from petroleum), m. p. 197°, *cyclo*hexane*spiro*-5-methyloxindole, colourless prisms (from petroleum), m. p. 164°, and *cyclo*hexane*spiro*-1-acetyl-5-methyloxindole, colourless prisms (from methanol), m. p. 144°, were prepared and found to be identical (mixed m. p.) with the compounds obtained by Betts and Plant (*loc. cit.*) from the 1-*o*- and 1-*p*-toluidino*cyclo*hexane-1-carboxylic acids.

cyclo*Hexane*spiro-5-*methoxyoxindole*.—The interaction of *p*-methoxyphenylhydrazine and *cyclo*hexanecarboxylic acid chloride under conditions similar to those described above gave NN'-*di*cyclo*hexanecarboxyl*-p-*methoxyphenylhydrazine*, colourless needles (from aqueous ethanol), m. p. 199° (Found : C, 70·4; H, 8·5; N, 7·2. $C_{21}H_{32}O_3N_2$ requires C, 70·4; H, 8·4; N, 7·8%), but, when the acid chloride in ether was added to the hydrazine (3 mols.), the p-*methoxyphenylhydrazide* of the acid, colourless needles (from aqueous ethanol), m. p. 164° (Found : C, 68·1; H, 8·3. $C_{14}H_{20}O_2N_2$ requires C, 67·7; H, 8·1%), was formed (yield, 65%). The latter was heated with quicklime as above, but it was not necessary to purify the product through its acetyl derivative. After the crude cyclo*hexane*-spiro-5-*methoxyoxindole* had been distilled under reduced pressure, it crystallised from benzene in colourless plates (yield, 28%), m. p. 226° (Found : C, 72·7; H, 7·7. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4%).

cyclo*Hexane*spiro-5-*amino-oxindole*.—After a mixture of *cyclo*hexane*spiro*-5-nitro-oxindole (3 g.; Betts, Muspratt, and Plant, *loc. cit.*), granulated tin (6 g.), and concentrated hydrochloric acid (18 c.c.) had been boiled under reflux until all the nitro-compound had dissolved and for a further ½ hour, the solution was cooled, filtered, and evaporated to dryness. The residue was dissolved in warm 0·1*N*-hydrochloric acid, the tin precipitated with hydrogen sulphide, and the filtered solution concentrated and made just alkaline with ammonia. The precipitated cyclo*hexane*spiro-5-*amino-oxindole* was dried, washed with a little hot light petroleum, and crystallised from aqueous ethanol, from which it separated in pale yellow prisms (58%), m. p. 175° (Found : C, 72·7; H, 7·1. $C_{12}H_{14}ON_2$ requires C, 72·2; H, 7·4%).

cyclo*Hexane*spiro-5-*chloro-oxindole*.—(*a*) The above amine (8·6 g.) in hydrochloric acid (100 c.c. of 20%) was diazotised at 5° with sodium nitrite (2·8 g.) in water (20 c.c.), and the solution gradually added with shaking to a cold solution of cuprous chloride prepared by dissolving copper carbonate

(5 g.) in concentrated hydrochloric acid (50 c.c.) and boiling the whole for 10 minutes with excess of copper turnings. After several hours, the mixture was heated on the steam-bath, and the cyclo*hexane*spiro-5-*chloro-oxindole* which separated was obtained from aqueous ethanol in yellow needles (yield, 52%), m. p. 188° (Found: C, 66·0; H, 5·9. $C_{13}H_{14}ONCl$ requires C, 66·2; H, 5·9%). When this substance (0·5 g.) was refluxed for an hour with acetic anhydride (5 c.c.) and the mixture shaken with water, cyclo*hexane*spiro-1-*acetyl*-5-*chloro-oxindole*, pale yellow needles (from ethanol), m. p. 154°, separated (Found: C, 65·3; H 5·9. $C_{15}H_{16}O_2NCl$ requires C, 64·9; H, 5·8%).

(*b*) Prepared from the appropriate hydrazine by the usual process (above), the p-*chlorophenylhydrazide* of *cyclo*hexanecarboxylic acid separated from ethanol in colourless needles (yield, 73%), m. p. 176° (Found: C, 61·3; H, 6·6. $C_{13}H_{17}ON_2Cl$ requires C, 61·8; H, 6·7%). It was converted into the corresponding oxindole by a procedure similar to that used for *cyclo*pentane*spiro*oxindole, but the crude product, after distillation under reduced pressure, could not be made to crystallise. The syrup was accordingly refluxed for an hour with acetic anhydride, the mixture shaken with an excess of aqueous sodium carbonate, the oil extracted with ether, and the extract evaporated. The residue solidified when rubbed with ethanol, and *cyclo*hexane*spiro*-1-acetyl-5-chloro-oxindole separated from that solvent in pale yellow needles, m. p. 154°. On hydrolysis with aqueous ethanolic potassium hydroxide, it gave *cyclo*hexane*spiro*-5-chloro-oxindole, which crystallised from aqueous ethanol in yellow needles (yield, 25%), m. p. 188°. The latter and its acetyl derivative proved to be identical (mixed m. p.) with the substances described above under (*a*).

5-Acetyl-3 : 3-*dimethyloxindole*.—A mixture of 3 : 3-dimethyloxindole (3·2 g.; Brunner, *Monatsh.*, 1897, **18**, 95), aluminium chloride (10 g.), acetyl chloride (5 g.), and carbon disulphide (50 c.c.) was refluxed for 2½ hours, the solvent removed, and the residue added to ice–dilute hydrochloric acid. When the product was crystallised from aqueous ethanol, *5-acetyl*-3 : 3-*dimethyloxindole* was obtained in colourless prisms (yield, 72%), m. p. 196° (Found: C, 71·0; H, 6·5. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4%). After it had been refluxed for an hour with five times its weight of acetic anhydride, and the solution shaken with an excess of water, 1 : 5-*diacetyl*-3 : 3-*dimethyloxindole*, colourless plates (from ethanol), m. p. 136°, was precipitated (Found: C, 68·4; H, 6·1. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1%). It was hydrolysed to the former substance by boiling aqueous-ethanolic potassium hydroxide.

Oxime of 5-Acetyl-3 : 3-*dimethyloxindole*.—After 5-acetyl-3 : 3-dimethyloxindole (2 g.) and a mixture of hydroxylamine hydrochloride (4 g.) with crystallised sodium acetate (8 g.) in water (30 c.c.) had been refluxed for 2 hours with sufficient ethanol to effect solution, the addition of water precipitated the *oxime*, colourless prisms (yield, 95%; from benzene), m. p. 196° (Found: C, 65·6; H, 6·2. $C_{12}H_{14}O_2N_2$ requires C, 66·1; H, 6·4%). When a solution of the oxime (1 g.) in concentrated sulphuric acid (10 c.c.) was heated on the steam-bath for an hour, cooled, poured on ice, and made alkaline with ammonia, 5-acetamido-3 : 3-dimethyloxindole, colourless plates (yield, 95%; from water), m. p. 261°, was obtained (Found: C, 66·2; H, 6·6. Calc. for $C_{12}H_{14}O_2N_2$: C, 66·1; H, 6·4%). After the latter had been refluxed for 2 hours with an excess of sulphuric acid (40%), and the cold solution neutalised with ammonia (cooling), 5-amino-3 : 3-dimethyloxindole, colourless prisms (from benzene), m. p. 184°, was precipitated. It proved to be identical (mixed m. p.) with a specimen of the base prepared by reduction of 3 : 3-dimethyl-5-nitro-oxindole as described by Brunner (*loc. cit.*).

3 : 3-*Dimethyloxindole-5-carboxylic Acid*.—5-Acetyl-3 : 3-dimethyloxindole (2 g.) was gradually added to potassium hydroxide (20 g.) which had been melted by heating with water (2 c.c.). The whole was heated with stirring for a further ½ hour, and, when cold, it was dissolved in water, and the solution boiled with charcoal. After filtration, addition of hydrochloric acid precipitated 3 : 3-*dimethyloxindole-5-carboxylic acid*, colourless needles (yield, 40%; from aqueous ethanol), m. p. 297° (Found: C, 64·2; H, 5·2. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4%).

cyclo*Hexane*spiro-5-*acetyloxindole*.—Prepared from *cyclo*hexane*spiro*oxindole in a manner similar to that described above for 5-acetyl-3 : 3-dimethyloxindole, cyclo*hexane*spiro-5-*acetyloxindole* crystallised from aqueous ethanol in colourless plates (yield, 66%), m. p. 192° (Found: C, 74·4; H, 6·9. $C_{14}H_{17}O_3N$ requires C, 74·1; H, 7·0%). Its *oxime* separated from aqueous ethanol in colourless plates (yield, 95%), m. p. 212° (Found: C, 69·9; H, 7·0. $C_{14}H_{18}O_3N_2$ requires C, 69·8; H, 7·0%). When this was heated with concentrated sulphuric acid as described above for the related oxime, cyclo*hexane*spiro-5-*acetamido-oxindole*, colourless needles (yield, 95%; from aqueous ethanol), m. p. 298°, was obtained (Found: C, 70·2; H, 7·1. $C_{14}H_{18}O_3N_2$ requires C, 69·8; H, 7·0%). The substance was hydrolysed by refluxing it with 40% sulphuric acid and, when the product obtained by precipitation with ammonia was crystallised from aqueous ethanol, *cyclo*hexane*spiro*-5-amino-oxindole was obtained in pale yellow prisms, m. p. 175°, identical (mixed m. p.) with the compound described above.

The authors are indebted to Professor Sir Robert Robinson, O.M., F.R.S., for his interest in these investigations.

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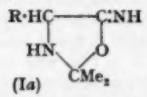
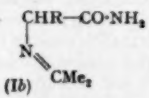
768. *The Interaction of α-Amino-nitriles and Aldehydes and Ketones.*

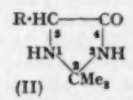
By A. C. Davis and A. L. Levy.

α-Amino-nitriles react with aldehydes to give Schiff's bases, which may isomerise to glyoxalines, and with ketones in the presence of sodium alkoxides to give 5-imino-oxazolidines or Schiff's bases of the corresponding α-amino-amides (I). The latter rearrange, when heated, to the little known tetrahydro-4-ketoglyoxalines (II), whose acylation, alkylation, and coupling with diazo-compounds are studied. The compounds (I) and (II) react with aromatic aldehydes to give α-arylideneamino-amides, except in the case of benzaldehyde and (II) which give derivatives of β-phenylserine. The reactions of *N*-methylaminoaceto-nitrile and -amide with aldehydes and ketones are also studied. Preliminary attempts are made to synthesise benzyldethiopenillonic acid, and some general observations on the reactions between carbonyl compounds and α-amino-acid derivatives are recorded.

Cook, Heilbron, and Levy (*J.*, 1948, 201) described the reaction of acetone with aminoacetonitrile in the presence of a catalytic quantity of sodium ethoxide. The highly crystalline product, which was formulated as 5-imino-2 : 2-dimethyloxazolidine (I*a*; R = H), was shown to be readily hydrolysed by cold water to aminoacetamide and acetone. In the present paper, the generality of this reaction of α-amino-nitriles, and other aspects of the chemistry of the products derived from it, are examined.


(I*a*)


(I*b*)

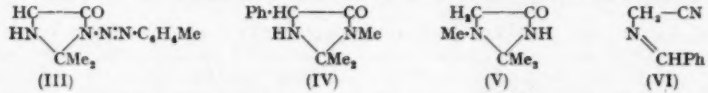

(II)

It has been shown (Cook, Heilbron, and Mahadevan, *J.*, 1949, 1061) that α-amino-α-phenylacetonitrile similarly condenses with dry acetone in the presence of sodium methoxide, the crystalline product (I*a*; R = Ph) being hydrolysed by water in an analogous fashion to α-amino-α-phenylacetamide and acetone. A corresponding compound (I*a*; R = Me) was obtained from α-aminopropionitrile and acetone (Cook and Levy, *J.*, 1950, 642), though aminocyanoacetic ester has not been induced to react. The products of these reactions were labile, and all attempts to prepare hydrochlorides or picrates led to the salts of the corresponding α-amino-amides. The fission of the oxazolidine (I*a*; R = H) by water, leading to aminoacetamide and acetone, has been found to be an equilibrium reaction which can be driven in one or the other direction by removing the acetone or the water. When treated with hydrogen sulphide, (I*a*; R = H) gave aminoacetamide and thioacetone. Further, aceturamide and α-acetamido-α-phenylacetamide were the only isolatable products from attempts to acetylate the imino-oxazolidines (I*a*; R = H or Ph). These results seem to indicate the Schiff's base (I*b*) as a better formulation, though in this case the cyclic structure (I*a*) would doubtless be its precursor. Chemical evidence is at present insufficient to allow a final decision between (I*a*) and (I*b*) (the tautomeric 5-amino-2 : 2-dimethyloxazoline structure seems far less likely), which must await accumulation of further physical data. A similar problem was encountered by Cope and Hancock (*J. Amer. Chem. Soc.*, 1942, **64**, 1503; 1944, **66**, 1453, 1738, 1747) during a study of the readily hydrolysed condensation products of aldehydes and ketones with α-amino-ethanols. From consideration of molecular refractivities they concluded that either oxazolidines or Schiff's bases could be formed, depending on the nature of the substituents. From infra-red spectroscopic work by Daasch and Hanninen (*ibid.*, 1950, **72**, 3673) it appears that the corresponding condensation products from aromatic aldehydes have the Schiff's base structure.

When *cyclo*hexanone was condensed with aminoacetonitrile at 90—100° with a sodium methoxide catalyst, the product was differed from the corresponding acetone compound (I; R = H), in so far as it formed a stable acetyl derivative and a picrate and was not hydrolysed by water. It was then found that when both the compounds (I; R = H or Ph) were heated, suitably in pyridine, they rapidly rearranged to more stable compounds which formed crystalline hydrochlorides and picrates and were readily monoacetylated; the rearranged bases can thus

be formulated with some certainty as tetrahydro-4-ketoglyoxalines (II; R = H or Ph). This isomerisation is reversible, in the case of (II; R = H), which appears to undergo partial reconversion into (I; R = H) on fusion or in hot pyridine. The *cyclo*hexanone product, also, is regarded as a tetrahydroketoglyoxaline (II; R = H; $[CH_2]_5$>C in place of Me_2C), its production doubtless resulting from the high temperature of the reaction. Rearrangement in the case of (I*a*) is paralleled by the stages which are thought to occur during the Bucherer reaction (see, *e.g.*, Cook, Heilbron, and Levy, *J.*, 1947, 1589), or in the case of (I*b*) involves addition of the amide group to the Schiff's base linkage.

Unlike the primary products (I), the glyoxaline derivatives (II; R = H and Ph) were not hydrolysed by cold water, and only slowly by boiling water. For complete hydrolysis of (II; R = H) cold concentrated alkali was effective, but the phenyl analogue (II; R = Ph) required refluxing with this reagent. Both were hydrolysed rapidly by hot dilute acid. α-Aminoamides were formed in the hydrolyses, but not quantitatively owing to their instability under such conditions. The primary products (I) and the glyoxalines (II) were conveniently differentiated by their behaviour towards 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid: the former gave an immediate yellow precipitate of acetone 2 : 4-dinitrophenylhydrazone whereas the latter were stable. Tetrahydro-4-keto-2 : 2-dimethylglyoxaline (II; R = H)

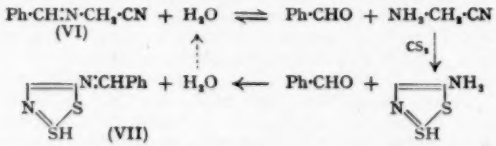


(III) (IV) (V) (VI)

coupled with toluene-*p*-diazonium chloride to give a colourless crystalline derivative containing an incipient diazonium group, for, when treated with a phenol, acidified and then made alkaline, it gave a precipitate of azo-dye. The compound was stable towards cold alkali, but with warm dilute hydrochloric acid lost nitrogen and yielded *p*-cresol; it is formulated as the 3-*p*-tolueneazo-compound (III), since the 1 : 2 : 2-trimethylglyoxaline derivative also coupled with diazonium salts. Tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline (II; R = Ph) was unaffected by diazomethane, but with methyl sulphate and sodium hydroxide gave a monomethyl derivative. As this afforded α-amino-α-phenylacetic acid on hydrolysis, it is the 2 : 2 : 3-trimethyl compound (IV). However, attempts to cause the compounds (II; R = H or Ph) to react similarly with α-bromo-acids or -esters, and thereby to establish a new route to dipeptides, were unsuccessful. The phenyl compound (II; R = Ph) was also unaffected by diazoacetic ester at 110°.

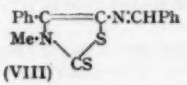
Methylaminoacetonitrile has been shown to condense with acetone in the presence of sodium methoxide, to give a 1 : 1 addition product (Cook and Cox, *J.*, 1949, 2337). This was not hydrolysed by cold hydrochloric acid, formed a stable picrate, and could not be rearranged by boiling bases or by fusion. We therefore prefer to regard it as tetrahydro-4-keto-1 : 2 : 2-trimethylglyoxaline (V) (contrast Cook and Cox, *loc. cit.*).

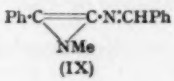
We shall consider next the reaction of aldehydes with α-amino-nitriles. Equimolecular quantities of benzaldehyde and aminoacetonitrile reacted exothermally in chloroform, one molecular proportion of water being eliminated. Distillation gave a colourless oil, which was readily hydrolysed to benzaldehyde by warm water and, from its analysis and light absorption

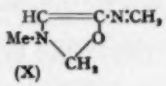


at 2580 Å is certainly to be formulated as *N*-benzylideneaminoacetonitrile (VI). On being kept for 6 weeks in a sealed tube, this partly changed to 2-phenylglyoxaline, obtained previously only from dinitrotartaric acid, benzaldehyde, and ammonia (Maquenne, *Ann. Chim. Phys.*, 1891, **24**, 543; Fargher and Pyman, *J.*, 1919, **115**, 232). Similarly, ethyl benzylideneaminocyanoacetate (not isolated) yielded on storage ethyl 2-phenylglyoxaline-4-carboxylate. This change is to be compared with the corresponding isomerisation of (XI) which may be presumed (see below) to occur in the Minovici preparation of 2 : 4-diphenylglyoxaline, though it was not accelerated by acid. When benzylidenaminoacetonitrile and carbon disulphide were kept together in technical ether, 5-benzylideneamino-2-mercaptothiazole (VII) soon separated, whereas in thoroughly dried ether no such reaction took place; the small quantity of water

present in technical ether presumably sets up an equilibrium between the Schiff's base and its components, whereupon the aminoacetonitrile reacts irreversibly with carbon disulphide giving 5-amino-2-mercaptothiazole; this will at once combine with the benzaldehyde to form (VII), liberating an equivalent quantity of water which repeats the cycle. In this connection, it has been observed that certain α-amino-nitriles decompose during distillation to compounds of the composition $R{\cdot}CH(NH_2){\cdot}CN + R{\cdot}CHO - H_2O$, which on treatment with carbon disulphide give rise to Schiff's bases of the corresponding aldehyde and 5-amino-2-mercaptothiazole (R = Me, Cook, Heilbron, and Levy, *J.*, 1947, 1598; R = C_9H_{13}, Cook, Heilbron, and Stern, *J.*, 1948, 2031). It appears, therefore, from the present work, that these distilled amino-

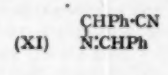

(VIII)

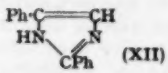

(IX)


(X)

nitriles are probably the Schiff's bases $R{\cdot}CH(N{:}CHR){\cdot}CN$ (cf. Delépine, *Bull. Soc. chim.*, 1909, **29**, 1184). This cannot apply, however, to an interesting compound obtained by distillation of α-methylamino-α-phenylacetonitrile, analysis of which indicates reaction of the nitrile with benzaldehyde with loss of water; this product affords the Schiff's base (VIII) with carbon disulphide; the structure (IX) has been proposed (Mahadevan, Thesis, London, 1948). Mention should also be made of a by-product isolated by Cook and Cox (*J.*, 1949, 2334) from the preparation of α-methylaminoacetonitrile, which gave methylaminoacetonitrile sulphate with sulphuric acid and from its analysis resulted by reaction with two additional molecules of formaldehyde with elimination of one of water. A possible structure for this compound is (X) (Cox, Thesis, London, 1949). It appears that this compound was first prepared and described by Dalgliesh and Mann (*J.*, 1947, 658), following an early preparative method for methylaminoacetonitrile, and was believed by them to be the nitrile itself. In spite of their further preparation from this material of salts of the true nitrile, the physical properties recorded (b. p. 95—105°/0·2 mm.) show that it was in fact Cook and Cox's formaldehyde condensation product (b. p. 90°/0·1 mm.), since methylaminoacetonitrile boils at 65°/19 mm.

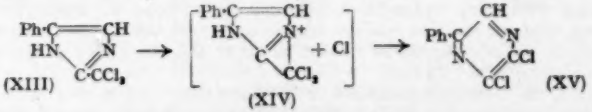
Benzaldehyde and α-amino-α-phenylacetonitrile are already known (Plochl, *Ber.*, 1881, **14**, 1143) to yield α-benzylideneamino-α-phenylacetonitrile (XI). The compound has alternatively been called " benzoylazotide " and " hydrocyanbenzide," and has been made also by the action


(XI)


(XII)

of ammonium cyanide on benzaldehyde (Snape and Brooke, *J.*, 1897, **71**, 529). However, when hydrogen chloride is passed into an ethereal solution of α-amino-α-phenylacetonitrile and benzaldehyde, 2 : 5-diphenylglyoxaline hydrochloride (XII) (cf. Haines and Wagner, *J. Amer. Chem. Soc.*, 1949, **71**, 2793) is produced (Minovici, *Ber.*, 1896, **29**, 2097). We have found that attempted distillation of the Schiff's base (XI) gave the glyoxaline (XII), which was also produced in impure form by distillation of α-amino-α-phenylacetonitrile at 0·05 mm., although in a high vacuum the nitrile sublimed unchanged.

Chloral reacted vigorously with aminoacetonitrile (charring occurred in the absence of a diluent), to give a crystalline product, m. p. 81°, analysis of which indicated a formula $Cl_3C{\cdot}CHO + NH_2{\cdot}CH_2{\cdot}CN$. It was not hydrolysed by water, and formed a stable picrate;


(XIII) (XIV) (XV)

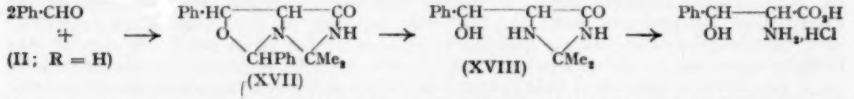
its structure is not known. It is of interest that Minovici and Bente (*Bul. Chim.*, 1915, **17**, 161) claimed that condensation of chloral with α-amino-α-phenylacetonitrile gave 5-phenyl-2-trichloromethylglyoxaline (XIII), which then rearranged, with loss of hydrogen chloride, to 2 : 3-dichloro-5-phenylpyrazine (XV). The mechanism of this change may well involve the bicyclic immonium salt (XIV), as in the interesting ring expansion of 2-chloromethyl-1-ethylpyrrolidine to 3-chloro-1-ethylpiperidine noted by Fuson and Zirkle (*J. Amer. Chem. Soc.*, 1948, **70**, 2760).

In order to ascertain whether the compounds (I), (II; R = H), and (V) possessed active methylene groups, allowing their use in amino-acid syntheses as with 2-phenyloxazolone, hydantoin, rhodanine, 2-mercaptothiazolone, etc., their reactions with aromatic aldehydes were investigated. When (I; R = H) was warmed with benzaldehyde, acetone was evolved and a crystalline product readily obtained, whose analysis indicated replacement of acetone by benzaldehyde. It was a labile substance, being readily hydrolysed by warm water to benzaldehyde and aminoacetamide, though resynthesised when these substances were combined in ethanol. It showed light absorption maxima at 2510 and 2560 Å, characteristic of the grouping Ph·CH:N, and is, therefore formulated as the Schiff's base *N*-benzylideneaminoacetamide (XVI; R = H). The reaction was catalysed by water, and may be represented as:

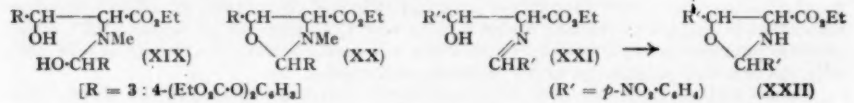
$$CMe_2{:}N{\cdot}CHR{\cdot}CO{\cdot}NH_2 + H_2O \rightleftharpoons COMe_2 + NH_2{\cdot}CHR{\cdot}CO{\cdot}NH_2 \overset{Ph{\cdot}CHO}{\rightleftharpoons} CHPh{:}N{\cdot}CHR{\cdot}CO{\cdot}NH_2 + H_2O$$
(XVI)

The phenyl compound (I; R = Ph) reacted similarly, the product (XVI; R = Ph) being in this case already known (Clarke and Francis, *J.*, 1911, **99**, 320). Attempts to cyclise the products (XVI; R = H or Ph) failed.

The glyoxaline derivative (II; R = H) and benzaldehyde, when warmed together, gave a crystalline product (XVII) in good yield; analysis indicated addition of two molecules of benzaldehyde to one of the glyoxaline with elimination of water. With cold hydrochloric acid, it readily lost one molecule of benzaldehyde, giving the hydrochloride of a base (XVIII), which was converted by 12 hours' refluxing with ethanolic hydrogen chloride into β-phenylserine ethyl ester hydrochloride. This series of reactions is, therefore, formulated as follows:



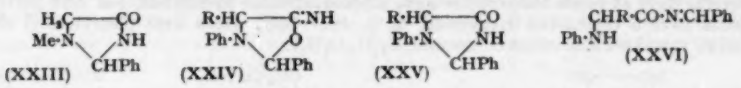
These reactions are closely comparable with the condensation of 3 : 4-di(ethyl carbonato)-benzaldehyde with sarcosine ester in the presence of sodium (Dalgliesh and Mann, *J.*, 1947, 658), in which two molecules of the aldehyde were consumed to give an intermediate product, readily hydrolysed by acid to a substituted phenylserine ester. This intermediate was formulated as (XIX) by Dalgliesh and Mann (*loc. cit.*); but a better expression would appear to be (XX), comparable with the oxazolidine (XVII) above, particularly as Dalgliesh (*J.*, 1949, 90) has made the interesting observation that the Schiff's base (XXI) isomerises in ethanol to the oxazolidine (XXII). Compounds analogous to (XXI) have also been made by the action of aromatic aldehydes on glycine in alkaline solution (Erlenmeyer and Bade, *Annalen*, 1904, **337**, 222; Gulland and Mead, *J.*, 1935, 210) and on glycine ester in the presence of sodium (Rosenmund and Dornsaft, *Ber.*, 1919, **52**, 1734).



The compound (II; R = Ph) also condensed readily with benzaldehyde, to give a pale yellow, highly crystalline product, which was considerably more stable than (XVII), for 36 hours' refluxing with 20% hydrochloric acid merely afforded its hydrochloride. Analysis showed, indeed, that the reaction was not analogous to that taking place in the glycine series, since the product had a composition corresponding to (II; R = Ph) + 2Ph·CHO − H_2O − Me_2CO. Its structure is not known.

The reaction of tetrahydro-4-keto-1 : 2 : 2-trimethylglyoxaline (V) with benzaldehyde followed the same course as that of (I), acetone being expelled and a compound obtained, which is probably to be formulated as (XXIII). Thus it was more stable than the Schiff's bases (XVI) and could be recrystallised from hot water. It gave benzaldehyde 2 : 4-dinitrophenylhydrazone with Brady's reagent only after boiling, and was unchanged after one hour's refluxing in pyridine. An imino-structure cannot be entirely dismissed, however; but a benzylideneamide expression such as (XXVI) (see below) is excluded, as the compound did not show the required characteristic ultra-violet absorption. The same substance was produced by condensation of benzaldehyde with sarcosine amide, and a higher homologue similarly from

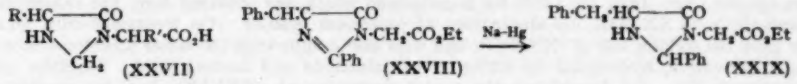
benzaldehyde and *N*-methylvaline amide. It is relevant in this connection that Miller and Plochl (*Ber.*, 1898, **31**, 2699) reported a general reaction between α-arylamino-nitriles and aromatic aldehydes in the presence of ethanolic potassium cyanide or hydroxide, leading to two isomeric compounds formulated by them as (XXVI). These could be reversibly interconverted by heating them in solvents, and in view of the present work are probably to be



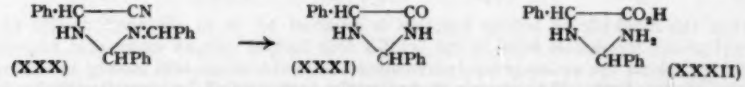
regarded as the 5-imino-oxazolidine (XXIV) and tetrahydro-4-ketoglyoxaline (XXV), although the possibility of *cis–trans*-isomerism of one cyclic structure also arises. Formally, structures such as (XXVI) are alternatives to (I) and (XVI), but the literature shows that such amide "Schiff's bases" are only produced in exceptional circumstances, compounds such as R'·CO·NH·CHR·OH and R'·CO·NH·CHR·NH·COR" being the normal products of interaction of an aldehyde and an amide (Agarwal, Pandya, and Tripathi, *J. Indian Chem. Soc.*, 1944, **21**, 283, and earlier papers in this series; cf. also Moscheles, *Ber.*, 1891, **24**, 1805). In some other cases where such alkylideneamides have been proposed, the compounds are better regarded as cyclic structures such as (XXV) (cf. Cornforth and Cornforth, *J.*, 1949, 1028).

It was noted by Erlenmeyer and Bade and by Dalgliesh and Mann (*locc. cit.*) that the formation of phenylserines by reaction of benzaldehydes with glycine or glycine ester was dependent on the substitution in the benzene ring, and it was therefore of interest to study the behaviour of anisaldehyde, piperonaldehyde, and salicylaldehyde towards our compounds (I), (II), and (V). In all cases, except that of (V) where it is not stoicheiometrically possible, the products were Schiff's bases of aminoacetamide or α-amino-α-phenylacetamide. Thus the behaviour of (II), in condensing with two molecules of benzaldehyde and giving rise to a derivative of phenylserine, is exceptional. With (V), compounds analogous to (XXIII) were produced.

The tetrahydro-4-ketoglyoxaline ring system does not appear to be well known, and we have so far found only four examples. The structure (XXVII) has been suggested by French and Edsall (*Adv. Protein Chem.*, 1945, **2**, 277) for the rather ill-defined compounds obtained by the action of formaldehyde on certain dipeptides (Franzen and Fellmer, *J. prakt. Chem.*, 1917, **95**, 299; Wadsworth and Pangborn, *J. Biol. Chem.*, 1936, **116**, 423).



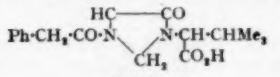
An interesting peptide synthesis involving a tetrahydroketoglyoxaline intermediate was effected by Granacher and Mahler (*Helv. Chim. Acta*, 1927, **10**, 248). The heterocyclic ring of 4-benzylidene-2-phenyloxazolone was opened with glycine ester, and then closed with alkali or phosphorus oxychloride to give the dihydroglyoxaline derivative (XXVIII). Reduction with sodium amalgam gave the tetrahydro-compound (XXIX), which was hydrolysed with loss of benzaldehyde to give phenylalanylglycine.



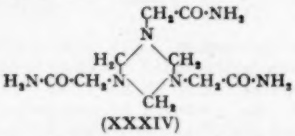
The third example (XXXI) arose from the action of hydrochloric acid on (XXX), obtained by the addition of one molecule of hydrogen cyanide to hydrobenzamide (Plochl, *Ber.*, 1880, **13**, 2118; 1881, **14**, 1139, 1316). An alternative α-lactam structure proposed by Plochl for (XXXI) now appears very unlikely. The compound formed a hydrochloride, and was said to be opened by aqueous ammonia to give the acid (XXXII), which was recyclised by heating to 100°; however, from its properties, (XXXII) may well be a hydrate of (XXXI).

The most important monocyclic tetrahydro-4-ketoglyoxaline, however, is benzyldethiopenillonic acid (XXXIII), which is obtained by the desulphurisation of the thermal rearrangement product of benzylpenicillin (methyl ester) ("The Chemistry of Penillicin," Oxford Univ. Press, 1949, p. 160), and some preliminary experiments towards its synthesis have been undertaken. Reaction of aminoacetamide with formaldehyde, in the hope of obtaining the parent

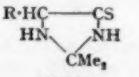
substance tetrahydro-4-ketoglyoxaline, gave a product, m. p. 162°, which appeared to be the trimer (XXXIV) because of its insoluble character, lack of NH_2-reactions, and ease of hydrolysis to formaldehyde (cf. the behaviour of aminoacetonitrile). Under other conditions the reaction leads to polymers (Marvel, Elliott, Boettner, and Yuska, *J. Amer. Chem. Soc.*, 1946, **68**, 1681). Treating *N*-hydroxymethyl-α-iodoacetamide with aqueous ammonia and ammonium carbonate for several days at room temperature gave aminoacetamide hydriodide, but with methanolic ammonia gave a crystalline hydriodide, m. p. 161—166°, which with phenylacetyl chloride and alkali gave an unidentified compound, $C_{12}H_{24}O_4N_2I$.



(XXXIII)



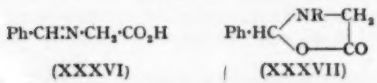
(XXXIV)



(XXXV)

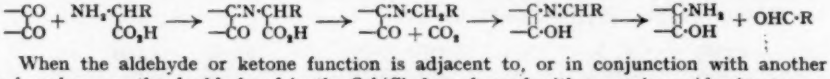
The corresponding 4-thiones (XXXV) have been investigated by Cook and Mahadevan (*loc. cit.*), and arise from the spontaneous condensation of acetone with α-amino-thioamides, or with α-amino-nitriles and hydrogen sulphide in the presence of pyridine.

The interaction of carbonyl compounds and amino-acid derivatives, generally, is a subject of great interest to the biochemist, and we conclude with a brief discussion of three aspects of this broader field, of which the present study forms a part. They are (*a*) the possible occurrence of cyclic forms of compounds hitherto thought to have open chains, (*b*) the trans-position of the double bond in Schiff's bases, resulting in loss of the α-amino-nitrogen atom, and (*c*) secondary interactions with the amino-acid side chains.



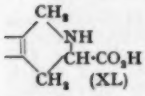
(XXXVI) (XXXVII) (XXXVIII) (XXXIX)

The compound benzylideneglycine arose as a by-product from the condensation of benz-aldehyde with glycine in the presence of acetic anhydride, acetic acid, and sodium acetate (Dakin, *J. Biol. Chem.*, 1929, **82**, 439), and was formulated as either (XXXVI) or (XXXVII; R = H). The structure (XXXVII; R = H) was independently proposed by Scheibler and Baumgarten (*Ber.*, 1922, **55**, 1358) for a compound which was obtained from the substituted amino-nitrile (XXXVIII)$_7$ by elimination of potassium cyanide. On treatment with alkali this gave the sodium salt of (XXXVI), and with acetic anhydride the latter afforded a mono-acetyl derivative, hydrolysed by water to benzaldehyde and aceturic acid. Scheibler and Baumgarten (*loc. cit.*) formulated the acetyl derivative as (XXXIX), but the expression (XXXVII; R = Ac) is clearly more satisfactory. This evidence, coupled with the fact that no other free acid such as (XXXVI) has yet been isolated (benzylidene-arginine and -lysine are stabilised by internal-salt formation), makes the cyclic structure (XXXVII; R = H) highly probable, though it is not certain whether this applies to Dakin's compound also.



When the aldehyde or ketone function is adjacent to, or in conjunction with another carbonyl group, the double bond in the Schiff's base formed with an amino-acid migrates, so that on hydrolysis the amino-group is transferred from the amino-acid moiety to that of the diketone or keto-acid. This process is frequently accompanied by decarboxylation at the α-unsaturated acid stage, and the formation of an aldehyde thus, from the corresponding amino-acid, has been termed by Schönberg, Moubasher, and Said (*J.*, 1948, 176) the Strecker degradation. This change may be brought about by a wide variety of carbonyl compounds, including many of natural origin such as sugars, vitamin K, alloxan, and dehydroascorbic acid, but the two most important examples are to be found in the ninhydrin (Ruhemann, *J.*, 1911, **99**, 1492) and the trans-amination reactions (Braunstein, *Adv. Protein Chem.*, 1946, **3**, 4). In the latter case, pyruvic, oxaloacetic, and ketoglutaric acids are chiefly implicated, and it appears to be the primary mechanism whereby amino-acids are degraded and synthesised *in vivo*. Similar deaminations may also be brought about in special circumstances with such simple compounds as benzaldehyde (Erlenmeyer, *Ber.*, 1871, **4**, 2896) and formaldehyde (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571).

α-Amino-group–side chain interactions chiefly concern the highly reactive formaldehyde molecule (French and Edsall, *loc. cit.*), though many of the examples are paralleled in the case of less versatile aldehydes and ketones. Thus serine and threonine yield oxazolidines, and cysteine a thiazolidine. Asparagine gives a hexahydropyrimidine, and phenylalanine, tyrosine, tryptophan, and histidine all receive a tetrahydropyridine ring fused to the aromatic nucleus, as shown in the partial formula (XL). The cross linking of free amino- with amide and guanidino-groups by formaldehyde is a prime cause of its tanning and hardening action on proteins (Fraenkel-Conrat and Olcott, *J. Amer. Chem. Soc.*, 1948, **70**, 2673).



(XL)

Experimental

5-Imino-2 : 2-dimethyloxazolidine.—Aminoacetamide (2·5 g.) in 50 c.c. of a mixture of acetone (320 c.c.) and benzene (80 c.c.) was heated under reflux for 30 minutes. The solution was then distilled slowly, with addition of the remainder of the solvent mixture to maintain a constant volume, and finally concentrated to 20 c.c. The colourless crystals (2·5 g.) which separated overnight had m. p. 85—90°. One recrystallisation from acetone gave 1·7 g. (50%) of nearly pure 5-imino-2 : 2-dimethyloxazolidine, m. p. 98°, undepressed by admixture with an authentic sample, which had m. p. 100—101°. The oxazolidine with picric acid in hot absolute ethanol gave *aminoacetamide picrate* in hair-like orange-yellow needles; on recrystallisation from ethanol the salt melted at 200° (Found : C, 32·0; H, 3·2. $C_9H_9O_9N_5$ requires C, 31·7; H, 3·0%). The oxazolidine (0·8 g.) in chloroform (10 c.c.) (dried over $CaCl_2$) was treated with acetic anhydride (1 c.c.) at room temp. to give, in 4 hours, crude aceturamide (0·4 g.), m. p. 132°, undepressed by admixture with a pure sample.

5-Imino-2 : 2-dimethyl-4-phenyloxazolidine.—The following procedure was found more satisfactory than that earlier described (Cook, Heilbron, and Mahadevan, *loc. cit.*). α-Amino-α-phenylacetonitrile (10 g.) was dissolved in acetone (30 c.c.) (dried over K_2CO_3). 1 C.c. of a solution of sodium (0·5 g.) in methanol (5 c.c.) was added and the mixture was kept for 15 minutes at 40—50°, this temperature being originally attained owing to the heat of reaction. After being kept for 1 hour at 0°, the colourless crystalline product (11 g., 80%) was collected, washed with acetone, and dried *in vacuo*; it had m. p. 144°. The oxazolidine was treated with picric acid in hot ethanol to give α-amino-α-phenylacetamide picrate, m. p. 195—200° (on recrystallisation from ethanol, 203—205°, undepressed by admixture with a sample prepared from α-amino-α-phenylacetamide). The imino-oxazolidine reacted vigorously with acetic anhydride containing 0·1% of sulphuric acid; cooling and dilution with benzene gave crystals of α-acetamido-α-phenylacetamide, m. p. 224°, undepressed by admixture with an authentic sample.

Tetrahydro-4-ketoglyoxaline-2-spirocyclo*hexane.*—To a mixture of aminoacetonitrile (40 g.) and *cyclo*hexanone (80 g.) (dried over K_2CO_3) was added dropwise a solution of sodium methoxide (as above) until a spontaneous rise in temperature was produced. The solution was kept for 15 minutes on the steam-bath, after which it solidified on cooling. Filtration, washing with a mixture of acetone (20 c.c.) and light petroleum (10 c.c.), and drying *in vacuo* gave the product (50 g., 45%) in fine crystals, m. p. 116°. On recrystallisation from chloroform–light petroleum, the *spiran* formed colourless needles, m. p. 121° (Found : C, 62·0; H, 9·0; N, 18·3. $C_8H_{14}ON_2$ requires C, 62·3; H, 9·15; N, 18·2%). Acetylation with acetic anhydride gave the *monoacetyl* derivative, which formed needles (from ethanol), m. p. 209—210° (Found : C, 61·2; H, 8·2. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2%). The picrate formed needles, m. p. 142°.

Tetrahydro-4-keto-2 : 2-dimethylglyoxaline.—5-Imino-2 : 2-dimethyloxazolidine (16 g.) and pyridine (8 c.c.) (dried over KOH) were heated together under reflux for 30 minutes; the solution was allowed to cool to 100° and poured into benzene (25 c.c.). After 2—3 hours at 0°, the product was broken up, filtered, and washed with benzene. The pale yellow crystals (11·8 g.; m. p. 120°), which contained some unchanged oxazolidine, were recrystallised from acetone, to give *tetrahydro-4-keto-2 : 2-dimethylglyoxaline* (9·3 g., 58%) in short colourless rods, m. p. 126° (Found : C, 52·7; H, 9·0; N, 24·8. $C_5H_{10}ON_2$ requires C, 52·6; H, 8·8; N, 24·5%). The rearrangement also occurred on refluxing in ethanol, but 3 hours' refluxing in acetone proved insufficient to effect it. The *hydrochloride*, precipitated by ether from a solution of the base in ethanolic hydrogen chloride, formed needles, m. p. 153°, on recrystallisation from ethanol–ether (Found : C, 39·6; H, 7·1; N, 18·1. $C_5H_{11}ON_2Cl$ requires C, 39·9; H, 7·4; N, 18·6%). The picrate, formed in aqueous, ethanolic, or acetone solution, had m. p. 123°. The acetyl derivative, formed readily with acetic anhydride, was first isolated as the *hemihydrate*, m. p. 70° (with resolidification, and remelting at 160°) (Found : C, 50·3; H, 8·0; N, 17·4. $C_7H_{12}O_2N_2,\frac{1}{2}H_2O$ requires C, 50·9; H, 7·9; N, 17·0%). Recrystallisation from benzene gave the anhydrous *monoacetyl* derivative, m. p. 160° (Found : C, 53·5; H, 8·0; N, 18·35. $C_7H_{12}O_2N_2$ requires C, 53·8; H, 7·8; N, 17·95%). Partial reverse rearrangement of the glyoxaline derivative was effected (*a*) by heating the fused base for a short time at 130—140° and (*b*) by heating, for 30 minutes under reflux, a solution of the derivative (0·5 g.) in pyridine (5 c.c.), followed by evaporation *in vacuo* which assured the absence of any acetone formed by hydrolysis. Either product, when dissolved in cold water and treated with 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid, gave a heavy precipitate of the acetone derivative, and gave a small yield of aminoacetamide picrate with ethanolic picric acid.

Tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline.—5-Imino-2 : 2-dimethyl-4-phenyloxazolidine (15 g.) and pyridine (30 c.c.) (dried over KOH) were heated under reflux for 15 minutes. After evaporation of the solvent, a single recrystallisation from ethyl acetate (75 c.c.) gave fine colourless needles (12·2 g., 81%) of *tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline*, m. p. 154° (Found : C, 69·4; H, 7·6; N, 15·1. $C_{11}H_{14}ON_2$ requires C, 69·5; H, 7·4; N, 14·7%). The compound was soluble in cold dilute hydrochloric acid, and reprecipitated by addition of aqueous sodium hydroxide, but the hydrochloride

could not be isolated in a crystalline state. Acetylation with acetic anhydride containing 0·1% of sulphuric acid gave readily the *acetyl* derivative, which formed clusters of short needles (from benzene), m. p. 182° (Found: C, 67·5; H, 7·0; N, 11·8. $C_{13}H_{14}O_3N_2$ requires C, 67·2; H, 6·9; N, 12·1%).

Hydrolysis of the Tetrahydroketoglyoxalines.—When tetrahydro-4-keto-2 : 2-dimethylglyoxaline was boiled with water for 10—30 minutes, copious evolution of ammonia and acetone occurred, but no crystalline product was isolated from the hydrolysate, which probably contained aminoacetamide and glycine. Therefore the glyoxaline (1 g.) and water (10 c.c.) were heated under reflux for 1 minute, cooled, and freed from acetone and water by evaporation *in vacuo*. The aminoacetamide was separated from unchanged starting material by precipitation with carbon disulphide from alcohol as the dithiocarbamate (0·5 g.) (Cook, Heilbron, and Levy, *J.*, 1948, 201), the yield of which indicated about 25% hydrolysis to aminoacetamide. In the course of attempts to condense (II; R = H) with α-bromo-acids, it was found that the compound was decomposed by cold caustic alkalis. Although decomposed at once by hot dilute hydrochloric acid to glycine, ammonia, and acetone, it was stable to cold acid. Tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline (II; R = Ph) was stable in the cold towards both acid and alkali. It was decomposed by 20% aqueous sodium hydroxide at 100° in 3 hours, yielding α-amino-α-phenylacetic acid, acetone, and ammonia. After hydrolysis in 2N-hydrochloric acid for 10 minutes under reflux, acetone was liberated; both α-amino-α-phenylacetamide hydrochloride (decomp. 210°, m. p. 270°) and α-amino-α-phenylacetic acid were isolated in low yield.

Coupling of the Tetrahydroketoglyoxalines with Toluene-p-diazonium Chloride.—*p*-Toluidine (2·1 g.) was diazotised in the normal manner with concentrated hydrochloric acid (5 c.c.) and sodium nitrite (1·37 g.) in water (5 c.c.). The solution was added slowly to a stirred suspension of potassium hydrogen carbonate (15 g.) in a solution of tetrahydro-4-keto-2 : 2-dimethylglyoxaline (2·24 g.) in water (50 c.c.) at 0°. After 1 hour, the pale pink crude product (2·75 g., 60%), m. p. 158—159°, was collected and washed with water. On crystallisation from *iso*propyl ether, *tetrahydro-4-keto-2 : 2-dimethyl-p-tolylazoglyoxaline* formed colourless needles, m. p. 163—164° (Found: C, 62·2; H, 7·1; N, 24·3. $C_{13}H_{16}ON_4$ requires C, 62·0; H, 6·9; N, 24·1%). The compound was soluble in cold 2N-sodium hydroxide, and was recovered on acidification; it was insoluble in cold mineral acid. Tetrahydro-4-keto-2 : 2 : 3-trimethylglyoxaline gave in the same way a poor yield of crude coupling product, m. p. 128—130°; it formed colourless needles, m. p. 131—132°, on recrystallisation from *iso*propyl ether. Both the azo-compounds were decomposed by warm dilute mineral acid to give *p*-cresol and nitrogen. When added to a solution of β-naphthol in aqueous sodium hydroxide, they produced only a faint tinge, but after acidification with concentrated hydrochloric acid, followed immediately by addition of excess of sodium hydroxide, a brilliant light red azo-compound was produced.

Methylation of Tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline.—This compound (1 g.), suspended in 10% aqueous sodium hydroxide (5 c.c.), was shaken with methyl sulphate (0·8 g.). It rapidly dissolved, and was replaced by a colourless oil which soon crystallised. The crude product (0·7 g., 64%) was washed with water and dried *in vacuo*; on recrystallisation from light petroleum (b. p. 80—100°), *tetrahydro-4-keto-2 : 2 : 3-trimethyl-5-phenylglyoxaline* formed thick colourless needles, m. p. 158—159° [Found: C, 70·7; H, 8·3; N, 13·6; *M* (Rast), 213. $C_{13}H_{16}ON_2$ requires C, 70·55; H, 7·9; N, 13·7%; *M*, 204]. This compound (1 g.) was hydrolysed by heating it for 2 hours under reflux with 20% hydrochloric acid (2·5 c.c.), α-amino-α-phenylacetic acid hydrochloride, m. p. 218—220°, separating on cooling. The free acid (subliming at 225°) also was obtained by neutralisation of the filtrate with sodium hydrogen carbonate.

No other *N*-alkyl derivatives of the tetrahydroketoglyoxalines or of their 3-acyl derivatives could be obtained by any method tried.

N-Benzylideneaminoacetonitrile.—Redistilled benzaldehyde (21·2 g.) was added to a solution of aminoacetonitrile (11·2 g.) in chloroform (20 c.c.), and the solution was set aside until the turbid liquid had separated into two layers (1 hour). The water (3·6 c.c.) was removed, and the chloroform layer was dried (Na_2SO_4), concentrated, and distilled *in vacuo*. The product (21·2 g., 74%), b. p. 92—93°/0·1 mm., was twice redistilled *in vacuo*. *N-Benzylideneaminoacetonitrile* formed a colourless, slightly viscous liquid, odourless when pure, n_D^{20} 1·5651 (Found: C, 74·9; H, 5·5; N, 19·6. $C_9H_8N_2$ requires C, 75·0; H, 5·6; N, 19·4%). Light absorption: $\lambda_{max.}$ 2580 Å; ε = 19,260. The compound decomposed slowly in moist air, producing benzaldehyde. It was miscible with organic solvents, and sparingly soluble in water; acidification of the solution gave an emulsion of benzaldehyde. Treatment with alcoholic hydrochloric or picric acid gave the corresponding salt of aminoacetonitrile. Ethereal hydrogen chloride produced a bulky colourless precipitate of the hydrochloride, which formed a deliquescent powder, m. p. 140° (decomp.), decomposed instantly by water to benzaldehyde.

Parallel reactions were carried out at room temperature between the Schiff's base (0·2 g.) and carbon disulphide (0·3 g.) in (*a*) commercial ether (*d* 0·720) and (*b*) ether (5 c.c.) thoroughly dried over sodium. Solution (*a*) developed a yellow colour in 5 minutes, and in 2 hours had deposited a quantity of thick yellow needles, m. p. 194—197° (decomp.); in 2 days solution (*b*) yielded none of this product, but had acquired a pale yellow colour. The product from (*a*) was recrystallised from methanol, to give bright yellow needles, m. p. 194—197°, of *5-benzylideneamino-2-mercaptothiazole* (Found: C, 54·9; H, 3·7; N, 12·5. $C_{10}H_8N_2S_2$ requires C, 54·5; H, 3·6; N, 12·7%). The thiazole was also prepared by warming 5-amino-2-mercaptothiazole (Cook, Heilbron, and Levy, *J.*, 1948, 201) with benzaldehyde in ethanol.

Benzylideneaminoacetonitrile did not appear to undergo any change when heated, a pure sample giving little distillation residue. A sample stored at 0° for 6 weeks, however, was found to have deposited a small quantity of hard, colourless prisms, m. p. 148—149°; after 10 months' storage, conversion appeared complete, giving a yellowish crystalline mass. Recrystallisation from ethanol gave colourless needles, m. p. 148—149°, of 2-phenylglyoxaline (Found: N, 19·9. Calc. for $C_9H_8N_2$: N, 19·4%). The Pauly test with diazotised sulphanilic acid was unsuccessful when applied to an aqueous

solution or suspension of the compound, but in aqueous-ethanolic sodium hydroxide the characteristic cherry-red colour developed slowly, and was changed to orange-yellow on acidification.

Similarly, benzaldehyde (3·2 g.) and ethyl aminocyanoacetate (4 g.), when set aside overnight in chloroform (20 c.c.), condensed with elimination of water; the oily Schiff's base (not isolated), when kept for 4 weeks in benzene, deposited colourless crystals (0·2 g.), m. p. 210°. The product, which formed colourless needles (from toluene), m. p. 225°, was almost certainly to be formulated, on the basis of analysis and a positive Pauly reaction, as *ethyl 2-phenylglyoxaline-4-carboxylate* (Found: C, 66·8; H, 5·8; N, 13·0. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6; N, 13·0%).

Condensation of Benzaldehyde with α-Amino-α-phenylacetonitrile.—α-Amino-α-phenylacetonitrile (10 g.) and benzaldehyde (9 g.) were kept overnight in chloroform (20 c.c.). The separated water (0·8 c.c., *ca.* 50%) was removed, and after drying and concentration the reaction mixture was distilled at 0·05 mm. After a low-boiling fraction (benzaldehyde), a reddish-yellow oil (4 g.) distilled at 160—170°. The distillation residue was an extremely viscous oil, which set to a mass of crystals, m. p. 265°, apparently crude lophine (2 : 4 : 5-triphenylglyoxaline, m. p. 275°, the highest-melting of the several thermal decomposition products of α-benzylideneamino-α-phenylacetonitrile; Beilstein's "Handbuch," Vol. XXIII, p. 318 and Vol. XIV, p. 469). The distillate crystallised slowly when kept in ether, giving prisms, m. p. 160—164°. On crystallisation from ethanol, the 2 : 4-diphenylglyoxaline formed needles, m. p. 164—166°, although on recrystallisation further from chloroform–methanol, the m. p. fell to 156—164° (Found: C, 81·55; H, 5·6; N, 12·15. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5; N, 12·7%). The isolation of this compound in three different forms, interconvertible by treatment with different solvents, was described by Haines and Wagner (*loc. cit.*). α-Amino-α-phenylacetonitrile when distilled at 0·05 mm. evolved water and ammonia, and gave a small yield of a light yellow oil, purified with ether–light petroleum to colourless prisms, m. p. 148—156°, undepressed on admixture with the sample of 2 : 4-diphenylglyoxaline of m. p. 164—166°. The bulk of the nitrile was converted into a resin. When heated at 50—60°/0·00001 mm., the nitrile (4 g.) sublimed to yield 1·5 g. of unchanged material, but the remainder again formed a hard resin.

Reaction of Aminoacetonitrile with Chloral.—Chloral (9 g.) was added slowly to aminoacetonitrile (3 g.) in chloroform (15 c.c.) with ice cooling. Dilution with benzene (5 c.c.) gave a mass of colourless leaflets (5 g.), m. p. 77—78°, which were collected and washed with ice-cold chloroform (5 c.c.). The addition *product* crystallised from benzene in colourless leaflets, m. p. 81° (Found: C, 24·2; H, 2·7; N, 13·55. $C_4H_5ON_2Cl_3$ requires C, 23·6; H, 2·5; N, 13·8%). On storage the compound decomposed completely in 3 months. The compound was treated with picric acid in aqueous ethanol to give the picrate in golden yellow platelets, m. p. 125°, strongly depressed on admixture with aminoacetamide picrate.

Reaction of 5-Imino-2 : 2-dimethyloxazolidine with Aromatic Aldehydes.—The oxazolidine (10 g.), benzaldehyde (redistilled) (13 g.), and water (1 drop) were heated together until an exothermic reaction commenced, and kept for 2 minutes at such a temperature that acetone slowly distilled from the mixture. After the residue had cooled to 100°, benzene (10 c.c.) was added. Cooling to 0° and further addition of benzene (*ca.* 10 c.c.) to the point of precipitation gave the Schiff's base (10·4 g., 73%) in colourless crystals, m. p. 125—126°. On recrystallisation from benzene, the *N-benzylideneaminoacetamide* formed short needles, m. p. 126° (Found: C, 66·7; H, 6·4; N, 17·0. $C_9H_{10}ON_2$ requires C, 66·7; H, 6·2; N, 17·3%). Light absorption in ethanol: $\lambda_{max.}$ 2510 Å, $\varepsilon = 17{,}010$; $\lambda_{inf.}$ 2560 Å, $\varepsilon = 15{,}390$. In the preparation of the Schiff's base, a small quantity of a by-product was usually obtained, forming colourless leaflets (from ethanol), m. p. 178—179°, which was found to be the water-soluble salt *carbamylmethylammonium benzoate* (Found: C, 55·3; H, 6·3; N, 14·1. $C_9H_{11}O_3N_2$ requires C, 55·1; H, 6·2; N, 14·3%). The reaction of 5-imino-2 : 2-dimethyloxazolidine with piperonaldehyde, *p*-anisaldehyde, or salicylaldehyde was effected by the same technique, using in each case 1 g. of the oxazolidine and 2·5 g. of the aldehyde. Thus, were obtained (3 : 4-*methylenedioxybenzylideneamino*)*acetamide* (58%), needles (from ethyl acetate), m. p. 185—186° (Found: C, 58·0; H, 4·9; N, 13·3. $C_{10}H_{10}O_3N_2$ requires C, 58·2; H, 4·9; N, 13·6%), α-*p-methoxybenzylideneaminoacetamide* (47%), felted needles, m. p. 153° (from ethanol) (Found: C, 62·2; H, 6·4. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·3%), and α-*N-o-hydroxybenzylideneaminoacetamide* (44%), short, very pale yellow needles (from ethyl acetate), m. p. 134°, which imparted a bright yellow colour to solvents (Found: C, 60·5; H, 6·0. $C_9H_{10}ON_2$ requires C, 60·7; H, 5·7%). Samples of the last and of the benzylidene compound were readily prepared, in low yield, by warming aminoacetamide with an equivalent quantity of the aldehyde, alone or in ethanol. All the Schiff's bases were broken down in 1—2 minutes by boiling water, to the aldehyde and aminoacetamide (isolatable as the picrate). In cold ethanol they formed crystalline picrates of indefinite m. p., passing into aminoacetamide picrate on recrystallisation. The benzylidene compound was unchanged by refluxing it with pyridine or acetic anhydride, although coloration and resinification occurred on treatment with acetic anhydride containing 0·1% of sulphuric acid.

Reaction of 5-Imino-2 : 2-dimethyl-4-phenyloxazolidine with Aromatic Aldehydes.—The oxazolidine (3 g.), salicylaldehyde (4·5 g.), and water (1 drop) were heated together until reaction commenced, and kept at the distillation temperature for 2 minutes. The solution was cooled, diluted with ethyl acetate (7·5 c.c.), and left at 0° until the crude α-*o*-hydroxybenzylideneamino-α-phenylacetamide (3·6 g., 90%) separated. The m. p. rose, on recrystallisation from methanol, from 148—150° to 151—152°, and was undepressed by admixture with a sample prepared as described by Clarke and Francis (*loc. cit.*). The benzylidene compound was also prepared from 5-imino-2 : 2-dimethyl-4-phenyloxazolidine, and proved to have m. p. 125—126° (corr.) and not 120—121° as found by the above authors (Light absorption: $\lambda_{max.}$ 2510, 2560 Å; $\varepsilon = 23{,}320$, 22,380).

Condensation of Tetrahydro-4-keto-2 : 2-dimethylglyoxaline with Benzaldehyde.—The glyoxaline (5 g.) and benzaldehyde (10 g.) were heated together under reflux for 5 minutes, cooled to 100°, diluted with benzene (10 c.c.), and left at 0° until separation of the crystalline product (5·05 g., 37%), m. p. 176—

179°, was complete. Recrystallisation from ethyl acetate gave the 2 : 3 : 4 : 5-*tetrahydro*-4-*keto*-2 : 2-*dimethyl*-2′ : 5′-*diphenyloxazolidino*(3′ : 4′-1 : 5)*glyoxaline* (XVII) in colourless needles, m. p. 187° (Found : C, 74·0; H, 6·8; N, 9·0. $C_{19}H_{20}O_2N_2$ requires C, 74·0; H, 6·5; N, 9·1%). The compound was stable to hot water, and decomposed very slowly in boiling aqueous sodium hydroxide, although instantly decomposed by mineral acid. The compound (XVII) (6·5 g.), and concentrated hydrochloric acid (15 c.c.) were heated for 1 minute on the steam-bath. On cooling, benzaldehyde was removed by extraction with carbon tetrachloride, and the aqueous layer was treated with potassium hydroxide (5 g.) in water (10 c.c.). After 10 minutes at 0°, the separated base, m. p. 178° (4·2 g., 91%), was collected and washed with water. On crystallisation from methanol, the *tetrahydro*-5-*α*-*hydroxybenzyl*-4-*keto*-2 : 2-*dimethylglyoxaline* (XVIII) formed colourless prisms, m. p. 178° (Found : C, 65·8; H, 7·3; N, 13·2. $C_{13}H_{16}O_2N_2$ requires C, 65·4; H, 7·3; N, 12·7%). The base formed a stable picrate, m. p. 159°, but the hydrochloride (formed in ethanol), m. p. 146—147°, decomposed in a desiccator. It was resistant to acetylation, and was recovered unchanged after 5 minutes' refluxing in concentrated hydrochloric acid.

β-Phenylserine Ethyl Ester.—The glyoxaline derivative (XVIII) (1·1 g.) and 20% ethanolic hydrogen chloride (10 c.c.) were heated together under reflux for 16 hours, cooled, and freed from ammonium chloride (0·24 g.) which had separated. The filtrate was evaporated to a syrup, taken up in absolute ethanol (3 c.c.), and filtered once more from ammonium chloride. On dilution with dry ether, the solution deposited a crystalline salt (1·1 g., 81%), m. p. 128—130°. On recrystallisation from ethanol–ether, the β-phenylserine ethyl ester hydrochloride formed cubical masses of colourless prisms, m. p. 134—135° (Found : C, 53·5; H, 6·7; N, 5·8. Calc. for $C_{11}H_{16}O_3NCl$: C, 53·8; H, 6·6; N, 5·7%). (Since the completion of this work, Hayes and Gever, *J. Org. Chem.*, 1951, **16**, 269, have described the preparation, from β-phenylserine, of the ethyl ester hydrochloride, m. p. 136—137°.) An ethanolic solution of the hydrochloride was treated with picric acid to yield the *picrate* of the ester in bright yellow needles, m. p. 156—157° (Found : C, 46·7; H, 4·5; N, 12·9. $C_{17}H_{18}O_{10}N_4$ requires C, 46·6; H, 4·1; N, 12·8%).

Condensation of Tetrahydro-4-*keto*-2 : 2-*dimethyl*-5-*phenylglyoxaline with Benzaldehyde.*—The glyoxaline (5 g.) and benzaldehyde (10 g.) were heated for 2 minutes under reflux. After cooling to 70—80°, the solution was diluted with methanol (15 c.c.) and kept at 0° until crystallisation was complete. The large yellow needles (4·7 g., 55%) were washed with methanol and dried in air. After crystallisation from ethanol the *substance* produced formed short pale yellow needles, m. p. 215° (Found : C, 81·0; H, 5·4; N, 8·6. $C_{22}H_{18}ON_2$ requires C, 80·8; H, 5·6; N, 8·6%). Crystallisation from ethyl acetate gave colourless felted needles, m. p. 225°, which had an identical analysis. The light yellow colour and lower m. p. were again observed on recrystallisation of this material from ethanol or aqueous ethanol. Prolonged refluxing with concentrated aqueous or ethanolic hydrogen chloride gave only the *hydrochloride*, m. p. 214° (Found : C, 73·2; H, 5·3; N, 7·8. $C_{22}H_{19}ON_2Cl$ requires C, 72·6; H, 5·5; N, 7·7%), from which the base was easily regenerated with pyridine in methanol. The picrate formed yellow needles, m. p. 170—171°.

Condensation of the Tetrahydroketoglyoxalines (II; R = H and Ph) *with Other Aldehydes.*—The compounds (II) were treated with salicylaldehyde, *p*-anisaldehyde, and piperonaldehyde, either by the technique employed for the 5-imino-oxazolidines, or in boiling pyridine, to give in moderate yields the appropriate Schiff's bases of (respectively) aminoacetamide and α-amino-α-phenylacetamide. The spiran described above also underwent this reaction, benzaldehyde in this case reacting as did other aromatic aldehydes to give the α-arylideneaminoacetamide. The compound (II; R = H) did not react with *cyclo*hexanone or phenylacetaldehyde under comparable conditions.

Reactions of Tetrahydro-4-*keto*-1 : 2 : 2-*trimethylglyoxaline and of α-Alkylamino-amides with Aldehydes.*—The glyoxaline (1 g.) and benzaldehyde (2·5 g.) were heated for 3 minutes under reflux with 1 drop of water, cooled, and treated with benzene (7 c.c.) and ice-cold light petroleum to the point of precipitation; after 1 day the colourless crystalline product (0·6 g., 39%) was collected, and washed with ether, and dried *in vacuo*; it then had m. p. 108—109°, unchanged on recrystallisation from light petroleum, which gave the 5-*imino*-3-*methyl*-2-*phenyloxazolidine* in plates (Found : C, 68·6; H, 6·8. $C_{10}H_{11}ON_2$ requires C, 68·2; H, 6·8%). The oxazolidine was hydrolysed very slowly by boiling water, or by cold 2N-hydrochloric acid, but immediately by hot mineral acid. Use of *p*-anisaldehyde (2 g.) similarly yielded 5-*imino*-3-*methyl*-2-p-*methoxyphenyloxazolidine* (1·4 g., 45%), m. p. 117—119°, which formed hexagonal plates, m. p. 117°, on recrystallisation from benzene (Found : C, 64·1; H, 6·7; N, 13·6. $C_{11}H_{14}ON_2$ requires C, 64·1; H, 6·8; N, 13·6%).

Sarcosine amide (1·8 g.), benzaldehyde (2·2 g.), ethanol (7 c.c.), and sodium ethoxide (trace) were heated under reflux for 3 hours. On concentration to 8—9 c.c., the solution commenced to deposit crystals; after 30 minutes in ice, the crystals were collected, and a second crop was obtained by evaporation (total : 3·1 g., 86%). Recrystallisation from light petroleum gave 5-imino-3-methyl-2-phenyloxazolidine, m. p. 108—109°, undepressed by the material prepared at above.

N-Methylvaline amide (2·6 g.), benzaldehyde (2·1 g.), ethanol (10 c.c.), and sodium ethoxide (trace) were heated under reflux for 3 hours and kept at 0° overnight. The product was obtained in two crops (total : 3 g., 70%) of large plates, m. p. 160—163°. On recrystallisation from ethanol, 5-*imino*-3-*methyl*-2-*phenyl*-4-*isopropyloxazolidine* formed platelets, m. p. 165—166° (Found : C, 71·7; H, 8·2; N, 13·1. $C_{13}H_{18}ON_2$ requires C, 71·5; H, 8·3; N, 12·8%).

Anilinoacetamide (Bischoff, *Ber.*, 1899, **22**, 1809) (1 g.), benzaldehyde (0·7 g.), methanol (15 c.c.), and sodium ethoxide (trace) were heated for 21 hours at 140°. On evaporation to 7 c.c. and storage for a short time in ice, the solution deposited the condensation product (0·55 g., 35%) in pale yellow needles, m. p. 218—220°; on recrystallisation from methanol the latter were obtained as short colourless rods, m. p. 222° (Found : C, 75·7; H, 5·95; N, 11·8. Calc. for $C_{15}H_{14}ON_2$: C, 75·6; H, 5·9; N, 11·8%). Light absorption in ethanol, $\lambda_{max.}$ 2420 Å; ε = 16,600. The compound did not depress the m. p. of a sample, m. p. 220°, prepared in poor yield from " anhydroformaldehydeaniline," benzaldehyde,

and potassium cyanide [Miller and Plochl, *loc. cit.*, recorded m. p. 219° and assigned the structure (XXVI; R = H)].

Condensation of Aminoacetamide and Formaldehyde.—Aminoacetamide (6·5 g.) in methanol (25 c.c.) containing sodium ethoxide (trace) was treated with gaseous formaldehyde, swept into the apparatus by a slow stream of nitrogen from a vessel in which paraformaldehyde (4 g.) was depolymerised by heat. The solution was cooled in ice during the reaction, after which the product crystallised when kept for 1 hour at 0°. The crude material (6·2 g., 82%) had m. p. 155—157°; recrystallisation from methanol gave the **1 : 3 : 5-*tri*(*carbamylmethyl*)*hexahydro*-1 : 3 : 5-*triazine*** (XXXIV) as colourless needles, m. p. 162° (Found: C, 42·5; H, 7·15; N, 32·55. $C_9H_{15}O_3N_6$ requires C, 41·85; H, 7·0; N, 32·55%). Determination of molecular weight by Rast's method was impossible owing to decomposition. No crystalline salts or acyl derivatives were formed; treatment with phenylacetyl chloride and aqueous sodium hydrogen carbonate gave phenaceturamide and formaldehyde.

α-Chloro-*N*-hydroxymethylacetamide (Einhorn, *Annalen*, 1906, **343**, 207) was treated with hot ethanolic ammonia, to yield ammonium chloride (nearly quantitatively) and an oily substance which could not be characterised. *N*-Hydroxymethyl-α-iodoacetamide (Einhorn, *loc. cit.*) (8 g.) was shaken with saturated aqueous ammonium carbonate (600 c.c.) and aqueous ammonia (*d* 0·880; 200 c.c.) until dissolved, and set aside for 10 days. The resulting solution was evaporated *in vacuo* at 50—55°; the residual syrup was treated with ethanol (25 c.c.) to give, in two crops (total, 5 g.), colourless cubical crystals of aminoacetamide hydriodide, m. p. 195°, raised to 200—203° on recrystallisation from acetic acid. The salt was soluble in water but sparingly soluble in ethanol or methanol, and oxidised on storage.

A solution of *N*-hydroxymethyl-α-iodoacetamide (4 g.) in saturated methanolic ammonia (50 c.c.) was kept for 2 days at room temperature. On evaporation, a semisolid mass remained, which yielded colourless cubical crystals (3·7 g.) of a hydriodide, m. p. 161—166°, on methanol–acetone recrystallisation. The m. p. remained indefinite on further crystallisation. The salt (1 g.) was treated with 10% sodium hydroxide (5 c.c.) and phenylacetyl chloride (0·4 g.) at 0° with shaking; in 10 minutes colourless plates (0·65 g.) separated, which had m. p. 167—170°. On recrystallisation from methanol, the *product* formed colourless octahedra, m. p. 173—174° [Found: C, 35·5; H, 6·35; N, 10·35; I (volumetric, as iodide), 31, 34. $C_{12}H_{24}O_4N_3I$ requires C, 35·8; H, 6·2; N, 10·4; I, 31·6%].

The authors express their gratitude to Sir Ian Heilbron, D.S.O., F.R.S., and to Dr. A. H. Cook, F.R.S., for their advice and encouragement, to the Department of Scientific and Industrial Research for a Senior Research Award (A. L. L.), and to the Rockefeller Foundation for a grant (A. C. D.).

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[*Received, August 25th*, 1951.]

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769. *Wood Starches. Part I.**

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The occurrence of starch in wood is discussed, together with methods of isolating and purifying sapwood starches.

The granular starch from elm sapwood has been shown to contain 20·5% of amylose. The methylated starch was hydrolysed and the products separated chromatographically, both on paper strips and on a cellulose column. The yield of tetramethyl glucopyranose (4·3%) indicates that in the amylopectin component there are 20 glucose residues per terminal group. This conclusion is supported by the results of oxidation with periodate.

BECAUSE of its characteristic colour reaction with iodine, starch is the most readily recognized reserve foodstuff of trees. It occurs for the most part in the form of simple granules measuring up to 10 μ in diameter and enclosed within specialized cells in leaves, stems, roots, and seeds. In woody stems starch is only rarely found in heartwood. In sapwood, however, it is frequently found in abundance in the parenchymatous tissue, a continuous system of living cells comprising laterally-arranged elements in the rays and vertically-arranged elements surrounding the sap-conducting vessels of hardwoods (wood parenchyma) and the resin-canals of softwoods (epithelium). It is only occasionally found in the lumina of dead cells such as the fibres of hardwoods. According to Phillips (*Forestry*, 1938, **12**, 15) the parenchymatous tissue of hardwoods can account, in some cases, for as much as 30% or more of the total tissue volume. In softwoods the proportion of parenchymatous tissue is, in the average, very much smaller than this. No entirely satisfactory analytical method for accurate determination of the amount of starch present in a sample of wood has so far been evolved. Estimated starch

* This paper was presented in abstract at the International Congress of Pure and Applied Chemistry in New York, September, 1951.

contents recorded in the literature vary from approximately 0·5 to over 5% of the dry weight of total wood substance. This wide range of results is not surprising when it is realized that the starch content of wood is subject to natural fluctuation. In the deciduous trees of the north temperate zone, for example, this fluctuation is seasonal, as demonstrated first by Cockerham [*Proc. Leeds Phil. Soc.* (*Sci.*), 1930, **2**, 64] for the wood of a 20-year old sycamore (*Acer pseudoplatanus*) by microscopical observations of thin sections. In general, starch content is minimal in early summer, and maximal in later summer. During the winter months it declines somewhat, but rises again to a maximum in spring just before the ascent of sap and bud burst.

The isolation of starch from wood for chemical study was first accomplished at the Forest Products Research Laboratory, Princes Risborough, in 1933 (*Rep. Forest Products Research Board*, H.M.S.O., London, 1933, **30**; 1934, 31) and the first wood starch preparations from the sapwood of oak and walnut were described by Campbell (*Biochem. J.*, 1935, **29**, 1068) in March 1935. In June of the same year Niemann, Roberts, and Link (*J. Biol. Chem.*, 1935, **110**, 727) presented their well-known paper on the isolation and characterization of a starch polysaccharide from the woody tissue of the apple tree. In all of these preparations and in others which followed, notably those of Sullivan (*J. Assoc. Off. Agric. Chem.*, 1935, **18**, 621) and of Spoehr and Milner (*J. Biol. Chem.*, 1936, **116**, 493), the native starch granules were first rendered soluble *in situ* and recovered in an amorphous form from wood extracts, various devices being used to remove soluble impurities such as tannins, colouring matters, and other polysaccharides extracted from the wood at the same time. It was early realized (Campbell, *Nature*, 1935, **136**, 299; Spoehr and Milner, *loc. cit.*) that prolonged extraction of wood with hot water gives rise to polysaccharide preparations resembling starch in their colour reaction with iodine but yielding uronic acids and xylose on acid hydrolysis in addition to glucose. In other words, such preparations are probably mixtures containing, in part, starch from the lumina of parenchyma cells and polyuronides from cell walls. That the prolonged action of hot water on wood substance brings about considerable chemical breakdown of the major cell-wall components of wood before all of the polysaccharides which stain blue with iodine are removed is shown by the data in the following Table.

Analysis of English oak sapwood (Quercus *sp.*) *before and after prolonged extraction with hot water renewed at 3-hourly intervals.*

(All results are expressed as percentages by weight of original, oven-dried wood.)

	Original wood	Residue after extraction with water: at 60° for 15 h.	at 100° for 27 h.*	at 100° for 117 h.†	at 100° for 141 h.‡
Loss in wt.	—	6·68	11·78	25·10	28·30
Sol. in cold water	4·68	0·29	0·31	0·76	0·12
Sol. in hot water	7·34	2·17	0·92	1·51	0·66
Sol. in 1% NaOH	22·54	15·92	14·87	17·53	16·18
C–B Cellulose §	51·46	51·05	50·99	44·88	40·78
Total pentosan	21·51	21·16	20·07	15·58	13·47
Pentosan in cellulose	12·51	11·73	11·68	7·14	5·34
Lignin	20·01	19·48	18·66	15·92	15·67
Total methoxyl	5·83	5·60	5·55	4·44	4·17
OMe in lignin	4·25	4·17	3·91	3·32	3·28
CO_2 as uronic anhydride	4·53	*b*	3·69	2·16	1·68

* Greater part of original starch and some polyuronides recovered from extracts (Campbell, *loc. cit.*).

† Starch and polyuronides recovered from extract (Spoehr and Milner, *loc. cit.*).

‡ Residue no longer gave starch reaction with iodine.

§ Cross and Bevan cellulose. *b* Not determined.

O'Dwyer (*Biochem. J.*, 1934, **28**, 2116; 1936, **31**, 254) has shown that, even after extensive extraction of oak sapwood with hot water to the point at which neither extract nor residue gives a blue colour with iodine, it is possible to extract with 4% aqueous sodium hydroxide a hemicellulose A which gives such a colour and yields small amounts of glucose on hydrolysis in addition to xylose and a methylated uronic acid. The presence of glucose residues in a hemicellulose extracted from mesquite wood was later established by Sand and Nutter (*J. Biol. Chem.*, 1935, **110**, 17). There may be some grounds, therefore, for the belief that there are close constitutional relations between the cell content starch of wood and the polyuronides of the cell walls, but it is now realized that the possible transformation of starch into

polyuronides and xylan is, on configurational grounds, not explicable on any such simple basis as the oxidation followed by decarboxylation *in situ* of primary alcoholic groups at the sixth carbon position of glucose residues (Campbell, *loc. cit.*).

In view of the realization that the true constitution of wood starch would be difficult, if not impossible, to determine on pre-solubilized material extracted from the wood with solvents, means were sought for the isolation of starch in its granular form. A simple technique was eventually evolved and the first 100 g. of grains were isolated from oak sapwood at Princes Risborough in 1939. The grains were of a pale buff colour due to occluded tannin, and the preparation contained a proportion of finely-divided fibrous cell wall material. Bleaching was effected by suspending the grains in chlorine water for 5 minutes, followed by treatment with sulphurous acid, and the products of chlorination were removed by cold 2% aqueous sodium sulphite. This treatment was repeated four or five times until no pink colour appeared after addition of sodium sulphite. Thorough washing with water, acetone, and ether yielded a pure white starch of $[\alpha]_D^{20}$ +154·8° (*c*, 0·47 in 0·1N-sodium hydroxide), containing 8—10% of finely divided cellulosic material. This starch was acid to litmus and could not be freed from acid by repeated washing. It has been suggested by Samec (*Monatsh.*, 1929, **53/54**, 852) that, when sulphurous acid is used in the bleaching of starches, a sulphonic acid group is introduced into the molecule.

Owing to the war, work was interrupted from the Autumn of 1939 until 1946 (*Rep. Forest Products Res. Board*, 1939—1947, 24). It was found later that the acid condition of this early starch preparation was responsible for some hydrolytic degradation during the long period of storage. In 1948, the technique for isolating granular starch from wood was improved and the structural investigations described below were carried out on fresh material from the elm (*Ulmus campestris*).

Microscopic examination of the elm sapwood starch revealed great variations in the shape of the granules, which ranged from roughly cubic and tetrahedral to spherical and dumb-bell shaped. The larger granules measured up to 10—12 μ along their longer axes. The starch was pale brown, owing to the adsorption of coloured impurities, and, together with a small proportion of fibrous material, probably included lignin, gallotannin, and anthocyanins. The view that lignin and gallotannin at least were merely incidental impurities is supported by the fact that, while some granules appeared not to absorb ultra-violet light of λ about 2800 Å, others manifested varying degrees of absorption. It thus seems that the granules were unevenly contaminated with the impurities, but it is difficult to decide whether these completely impregnated or merely encrusted the granules. We are indebted to Professor H. Erdtman and Dr. P. Lange of the Royal Institute of Technology, Stockholm, who prepared and interpreted the ultra-violet absorption photomicrographs.

The starch content of the air-dried sample of starch (moisture, 12·2; mineral ash, 0·96%) $[\alpha]_D$ +149° (*c*, 0·21 based on actual starch content, in 0·5N-sodium hydroxide) was determined by hydrolysis and paper-strip chromatography. Glucose was the only reducing sugar which could be detected and when estimated quantitatively (Flood, Hirst, and Jones, *J.*, 1948, 1679) accounted for 76·6% of the starch sample. An insoluble, flocculent, brown residue, probably lignin, which remained after hydrolysis of the sample, accounted for a further 4·6% of the total, the remaining 5—6% being represented mainly by the gallotannin impurity. The absence of uronic anhydride residues in the sample was demonstrated (method of Swenson, McCready, and McClay, *Ind. Eng. Chem. Anal.*, 1946, **18**, 290), the yield of carbon dioxide obtained (0·45%) having no structural significance (Campbell, Hirst, and Young, *Nature*, 1938, **142**, 912).

The gallotannin which appeared to be strongly adsorbed on the wood starch lattice was found to interfere seriously with many of the prescribed analytical techniques normally applied to starches. For example, during the dispersion of elm sapwood starch samples in potassium hydroxide solution prior to potentiometric iodine titration (Bates, French, and Rundle, *J. Amer. Chem. Soc.*, 1943, **65**, 142) for the assay of the amylose content, the associated gallotannin was atmospherically oxidized to ellagic acid. After neutralization of the disperison with hydrochloric acid (Wilson, Schoch, and Hudson, *ibid.*, p. 1381) and the addition of potassium iodide a pale purple colour soon developed which slowly intensified during the following hour. This effect was shown to be caused by the gradual liberation of free iodine by the oxidation of potassium iodide by ellagic acid. The lignin impurity also caused the same effect but to a quantitatively minor degree. In preparing the elm sapwood starch dispersions for potentiometric iodine titrations it was essential to remove this liberated iodine otherwise grossly low values for the amylose content would have resulted. This was accomplished

by the careful addition of dilute sodium thiosulphate solution until the purple colour was just discharged. Potentiometric iodine titrations were then conducted in the normal manner. Elm sapwood starch was thus shown to contain 20·5% of amylose. The efficacy of this procedure in providing results of the desired degree of accuracy was demonstrated when results identical within the limits of experimental error were obtained for the amylose content (18·7%) of a sample of barley starch before and after the addition of an authentic sample of gallotannin.

The blue value (0·337) (Hassid and McCready, *J. Amer. Chem. Soc.*, 1943, **65**, 1154) estimated for elm sapwood starch roughly confirms the amylose content as determined by the above modification to the prescribed procedure for potentiometric iodine titration. In the absence of definite figures for the blue values of the pure amyloses and amylopectins of wood starches, calculation of the amylose content from the blue value of elm starch is based on the arbitrarily chosen blue values of 1·35 for amylose and of 0·05 for amylopectin (Haworth, *J.*, 1946, 543). The blue value of 0·337 thus corresponds to an amylose content of 22·2%. An attempted purification of the starch by dispersion in sodium hydroxide solution (2N.) followed by neutralization and precipitation into alcohol yielded a product the blue value (0·311) of which corresponded to an amylose content of 20·2%.

The presence of an amylose component in elm sapwood starch was confirmed by its isolation as the butanol complex in typically spherocrystalline form (Schoch, *J. Amer. Chem. Soc.*, 1942, **64**, 2957). The fractionation procedure recommended by Higginbotham and Morrison (*J. Text. Inst.*, 1949, **40**, 208 T) was employed and the sample of amylose thus obtained was found to absorb 19·6% of its own weight of iodine as determined by potentiometric iodine titration. It is not claimed that this value represents that of the pure amylose component of elm sapwood starch. Further reprecipitations from butanol-saturated water would, no doubt, have increased the capacity of the product to absorb iodine, but continued efforts to purify the amylose were rendered impracticable by the relatively small quantity of wood starch available. However, the value of 19·6% uptake of iodine does at least approach that of 21·4—21·5% determined by Higginbotham and Morrison (*Chem. and Ind.*, 1947, **66**, 45) for pure amyloses from various sources.

The granular starch was methylated directly in the absence of air by the repeated application of methyl sulphate and concentrated sodium hydroxide solution (Hirst and Young, *J.*, 1939, 1471). The value of the methoxyl content of the product could not be increased beyond 44·1% (Calc. for $C_9H_{16}O_5$: OMe, 45·6%) by continued treatment with these reagents followed by fractionation from chloroform solution by the addition of light petroleum. Gallotannin and other coloured impurities had obviously been removed during methylation, to yield a snow-white derivative, $[\alpha]_D$ +208° (in chloroform), $\cdot\tau^{20}_{sp.}/c$ 3·0 (in *m*-cresol). Hydrolysis of the methylated starch and separation of the products on a paper chromatogram (Hirst, Hough, and Jones, *J.*, 1949, 928) indicated the presence of (*a*) 2 : 3 : 4 : 6-tetramethyl glucose, (*b*) 2 : 3 : 6-trimethyl glucose, and (*c*) two dimethyl glucoses, as well as faint traces of (*d*) a monomethyl glucose and of (*e*) glucose itself. The measured R_G values of the sugars corresponded reasonably well with the reported values, but confirmation of their identity was obtained by running authentic samples against the hydrolysate. Quantitative estimation of each of the major products of hydrolysis separated on a paper chromatogram was effected by hypoiodite oxidation in sodium hydroxide–phosphate buffer (pH 11·4; Ingles and Israel, *J.*, 1948, 810). The results indicated that of the total weight of the mixed methylated sugars obtained by hydrolysis of the methylated amylopectin component, some 5·3% was represented by tetramethyl glucopyranose, on the assumption that the methylated starch contained 20·5% of methylated amylose. The amylopectin of elm sapwood starch thus appears to contain 20 glucose residues per non-reducing terminal residue.

Confirmation of this result was obtained by separation of the hydrolysis products of the methylated starch, using a cellulose column (Hough, Jones, and Wadman, *J.*, 1949, 2511), two operations being necessary because of the resistance of the dimethyl and trimethyl methyl-glucosides to hydrolysis. The weights thus estimated of the various methylated sugars recovered from the columns were (from 2·17 g.) : 2 : 3 : 4 : 6-tetramethyl glucose, 0·0917 (±0·0032) g.; 2 : 3 : 6-trimethyl glucose, 1·7534 g.; 2 : 3-dimethyl glucose (?), 0·0886 g.; 3 : 6- and/or 2 : 6-dimethyl glucose (?), 0·1062 g.; monomethyl glucose and glucose obtained as a mixture, 0·0195 g. The total recovery was of the order of 95%. The limiting values (20 ± 1) for the number of glucose residues per non-reducing terminal residue in the amylopectin of elm sapwood starch were arrived at by calculations based on the upper and lower limiting values for the recovery of 2 : 3 : 4 : 6-tetramethyl glucose together, respectively, with the total actual and total possible recoveries of the methylated sugars from the columns.

The calculations were made on the assumptions that 20·5% of methylated amylose was present in the methylated starch and that the methylated amylose yielded 0·4% of tetramethyl glucopyranose on hydrolysis. Due allowance was also made for the effects of demethylation of tetramethylglucopyranose by the reagents used for the hydrolysis of the methylated starch to the mixture of free sugars. It was found that, under the conditions of hydrolysis, pure tetramethyl glucopyranose yielded 1·7% of trimethyl glucose.

An apparent molecular weight (approx. 5×10^5) for methylated elm sapwood starch was calculated from its viscosity measured in *m*-cresol ($\eta_{sp.}^{20}/c = 3$) (Hirst and Young, *loc. cit.*). An apparent value of about 2×10^5 was similarly calculated for the acetyl derivative ($CH_3 \cdot CO$, 44·9; calc. for $C_{12}H_{16}O_8$, 44·8%), $[\alpha]_D$ +167° (in chloroform), $\eta_{sp.}^{20}$ 0·32 (*c*, 0·47 in *m*-cresol) [by use of Staudinger's equation with the value $(0{\cdot}93 \times 10^{-4})$ of the constant k_m, given by Staudinger and Husemann (*Annalen*, 1937, **527**, 95)]. Some degradation of the polysaccharide probably occurred in this case, however, owing to the conditions of acetylation employed. Estimation of the reducing end-group of the unsubstituted starch by colorimetric measurement of the products of reduction of 3 : 5-dinitrosalicylic acid (Meyer, Noelting, and Bernfeld, *Helv. Chim. Acta*, 1948, **31**, 103) suggested a molecular weight of about $1{\cdot}2 \times 10^5$. This value was obtained for the sample of elm sapwood starch from which the impurities had been partly removed by dispersion in sodium hydroxide solution followed by neutralization and precipitation into alcohol. The apparent molecular weight obtained for the sample thus recovered is appreciably lower than the corresponding values of 2×10^5 and $2{\cdot}5 \times 10^5$ obtained for similarly treated potato and waxy maize starches respectively, but this may have been due to the persistence of a reactive impurity. An attempt was also made to estimate the reducing end-group by hypoiodite oxidation in a buffer medium (pH 10·6), but the results were rendered invalid by the presence of traces of gallotannin which was found to absorb iodine rapidly under the conditions of the experiment. It therefore appeared that, of the methods employed, viscosity determinations of the methyl derivative provided the most reliable data for the estimation of the molecular weight of elm sapwood starch.

It follows, therefore, that elm sapwood starch contains some 20% of amylose, that the amylopectin component possesses a high molecular weight, and that the proportion of non-terminal to terminal glucose residues in the latter component is approx. 20 : 1. Elm sapwood starch is thus constituted similarly in these respects to the majority of starch varieties for which data have been recorded. As with the amylopectins of other starches, it is clear that the amylopectin of elm sapwood starch possesses a branched-chain structure such as the so-called " laminated " structure (Haworth, Hirst, and Isherwood, *J.*, 1937, 578). The relatively high yield (9·5%) of dimethyl glucoses obtained by chromatographic separation of the products of hydrolysis of methylated elm sapwood starch is, however, at first sight inconsistent with such a formula. Only a small proportion of the yield of dimethyl glucoses could have arisen by demethylation of 2 : 3 : 6-trimethyl glucose during hydrolysis of the methylated starch, since pure 2 : 3 : 6-trimethyl glucose yielded only 1·5% of dimethyl glucoses under conditions identical with those used for the hydrolysis. The yield of dimethyl glucoses in excess of that which can be accounted for directly on the basis of a simple branched-chain structure probably arose, therefore, by undermethylation of the starch in the first place.

The periodate oxidation method of determining the proportion of terminal to non-terminal glucose residues in unmethylated starches (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27) was applied to granular elm sapwood starch. It was found that reliable results consistent with those provided by the end-group assay of the methylated starch were obtained only after the complete removal from the granules of the adsorbed gallotannin since this material was found to react with periodate to produce excessive quantities of acidic material. Removal of gallotannin was effected most efficiently without simultaneous degradation of the starch by repeated batchwise extraction of the granules with boiling 85% aqueous methanol (Schoch, *J. Amer. Chem. Soc.*, 1942, **64**, 2954). An aqueous solution of the extracted material gave reactions to tests applied for the detection of gallotannin. The residual granules retained their buff colour owing, probably, to the persistence of lignin which was also found to react with periodate with the formation of acidic material. However, direct compensation could be made for the quantity of acidic material liberated by the lignin during the periodate oxidation, by isolating a sample of lignin which was obtained as a flocculent, brown residue after complete acid hydrolysis of the starch and treating it with periodate under the same conditions. It was thus demonstrated that the amylopectin component of elm sapwood starch, on oxidation with periodate, liberated acidic material equivalent to one mole of formic acid per 20 glucose units, in agreement with the results of the methylation experiments.

Experimental.

Isolation of Granular Starch from Various Hardwoods.—Sapwood from trees freshly-felled between January and April was first converted into coarse sawdust and air-dried as rapidly as possible at room temperature. Rapid drying is necessary in order to kill the starch-bearing cells, Wilson (*Forestry*, 1935, **9**, 96) having emphasized that, even after a tree is felled, its parenchyma cells continue to live at the expense of their starch foodstuffs. Delay in drying of the wood may thus result in enzymic degradation or actual disappearance of the starch. The sawdust was then screened to remove particles larger than 20 mesh and smaller than 60 mesh. 200-G. batches of 20/60-mesh wood, suspended in 2·25 l. of cold water, were agitated with a high-speed propeller-type stirrer for approx. 45 minutes in order to dislodge the starch grains from open parenchyma cells. The liquor containing the starch grains was filtered off, made up to 2·25 l. with water, and added to a fresh batch of wood. Agitation was carried out as before and the various steps repeated using successive batches of wood up to 4 or 5 in number until a relatively concentrated suspension of grains was obtained. Filtration of this suspension through a Jena G.1, and subsequently a Jena G.2, sintered-glass filter was effective in separating relatively large wood particles and in yielding a starch suspension contaminated by a proportion of fine wood particles. By agitation with an excess of water and then storage, wood particles larger than the starch grains settled out first. When the supernatant liquor appeared to be free from wood, *i.e.*, after examination of samples at frequent intervals under the microscope, it was siphoned off and set aside to allow the starch grains to settle. This process of agitation with water, settling, and siphoning was repeated until all particles which settled more rapidly than starch grains were removed. After final settlement from suspension in water, the starch grains were washed with acetone, collected on a silk filter, washed with ether, and air-dried. Typical yields, on an oven-dried original wood basis, were 1·2% from English oak sapwood (*Quercus* sp.); 0·075% from maple wood (*Acer* sp.), and 0·16% from elm sapwood (*Ulmus campestris*). These yields are, of course, not quantitative, as much of the original starch remained enclosed in unruptured cells. The granular starch from oak contained about 8—10% and the elm starch approx. 7% of fibrous material insoluble in perchloric acid.

The starch grains isolated from the woods referred to above were buff-coloured owing to the occlusion of tannin and of other colouring matter such as anthocyanins which could not be removed by cold organic sovents. The influence of these and other impurities in the constitutional investigation of wood starch will be dealt with later.

Hydrolysis of granular wood starch with 12% hydrochloric acid gave rise to carbon dioxide in yields which in no case exceeded 0·5%. In accordance with previous findings this is without structural significance. It may, therefore, be concluded that the granular wood starches, although contaminated with particles of cell-wall material in loose admixture, are of true cell content origin and, unlike the solubilized starches described previously (Campbell, *Biochem. J.*, 1935, **29**, 1068), they contain no significant proportion of intimately admixed polyuronides derived from wood cell walls.

Properties of Elm Sapwood Starch.—Examination under the microscope revealed that only traces of fibrous material were admixed with the granules. The presence of anthocyanins in the preparation was indicated by treating the granules (0·2 g.) for 30 seconds with boiling ethyl-alcoholic hydrochloric acid (10 ml.; 1%) and then allowing the mixture to cool for 30 minutes. The pink colour which developed was replaced by a green colour on the addition of a slight excess of sodium hydroxide solution (Robinson and Robinson, *Biochem. J.*, 1929, **23**, 35; 1931, **25**, 1687). The gelation point of the starch was 54—55°. Above this temperature it formed with water a pale brown paste (1%) which was rather more mobile than potato starch paste (1%). The granules dispersed with some difficulty in N-sodium hydroxide, to give a solution which was deep brown owing mainly to the presence of gallotannin. The specific rotation, $[\alpha]_D^{19}$ +149° (*c*, 0·21 based on actual starch content, in 0·5N-sodium hydroxide), was determined with difficulty owing to the brown colour of the dispersion. The optical rotation was therefore also measured in solution in perchloric acid: $[\alpha]_D^{17}$ +191° (*c*, 0·51 in 4·8N-perchloric acid), to be compared with potato starch $[\alpha]_D^{17}$ +197° (*c*, 0·49 in 4·8N-perchloric acid). The gallotannin impurity was also responsible for a positive reaction of the starch to Fehling's test. A weak paste of the starch with water gave a deep blue colour with iodine solution. The colour was discharged by boiling the mixture but reappeared on cooling.

Hydrolysis.—The air-dried starch (11·31 mg.) was hydrolysed by heating it at 100° with sulphuric acid (0·5 c.c.; 5%) in a sealed tube for 6—7 hours. After neutralization with barium carbonate, only glucose could be detected on a paper-strip chromatogram. The glucose thus separated was estimated by the method of Flood, Hirst, and Jones (*loc. cit.*), with D-ribose as the reference sugar. The yield of glucose (9·63 mg.) accounted for 76·6% of the air-dried starch sample.

After larger-scale hydrolysis of the air-dried starch (0·1154 g.) with boiling sulphuric acid (10 c.c.; 5%) for 7 hours, a copious, flocculent, red-brown residue was collected on a Gooch crucible and dried to constant weight (5·3 mg., thus accounting for a further 4·6% by weight of the sample). The residue gave a positive reaction to Mäule's test (*Beiträge wiss. Bot.*, 1900, **4**, 166) for lignin. The optical rotation of the filtrate expressed in terms of the specific rotation of the calculated yield of glucose was $[\alpha]_D^{19}$ +51°

The yield of carbon dioxide obtained by decomposing the starch with boiling 12% hydrochloric acid for 4—5 hours (Swenson, McCready, and McClay, *loc. cit.*) was 0·45% by weight of the starch sample used.

The blue value measured at 20° and calculated on the basis of the actual starch content of the sample was 0·337 (Hassid and McCready, *loc. cit.*).

Potentiometric Determination of Amylose.—The method used was essentially that described by Bates, French, and Rundle (*loc. cit.*). The starch (19·94 mg.) was dispersed in potassium hydroxide (10 c.c.; 0·5N.), and the solution neutralized with hydrochloric acid (0·5N.) (Wilson, Schoch, and Hudson, *loc. cit.*). Potassium iodide (10 c.c.; 0·5N.) was added and the solution set aside with occasional gentle stirring for

1 hour. The purple colour which developed was easily discharged by the addition of sodium thiosulphate (5·44 c.c.; 0·001N.) and the volume made up to 100 c.c. with water. Potentiometric iodine titration of the resulting dispersion indicated that the amount of iodine taken up by 1 g. of starch was 0·044 g. If 21·5% is the amount of iodine taken up by pure amylose (Higginbotham and Morrison, *loc. cit.*), the amylose content of the sample of elm sapwood starch was 20·5%.

Separation of Amylose.—Granular elm sapwood starch (1·7 g.) was made into paste with hot water (30 c.c.) and added, with vigorous mechanical stirring, to a mixture of pyridine (30 c.c.) and water (40 c.c.) at 92° (Higginbotham and Morrison, *loc. cit.*). Some difficulty was experienced in dispersing the sample and, after 8 hours' stirring at 92°, there remained a copious, dark-brown residue (0·38 g.) which, moistened with water, gave a blue colour with iodine. Water (100 c.c.) at 90° was added to the hot, clear dispersion after centrifuging and the mixture allowed to cool undisturbed in a Dewar vessel for 6 days. The precipitated brown amylose–pyridine complex was separated at the centrifuge, washed well with cold, butanol-saturated water, and treated as described below. The brown centrifugate was evaporated under reduced pressure at 40° to a volume of 75 c.c., heated with animal charcoal for 20 minutes at 50°, and recentrifuged. The clear dispersion of elm sapwood amylopectin was precipitated into 95% alcohol (1 l.) and the residue after centrifuging dried *in vacuo* over calcium chloride, to give a fluffy, pale brown powder (0·75 g.; blue value, 0·13).

The moist amylose complex was dispersed in butanol-saturated water (200 c.c.) at 90°. The dispersion was centrifuged while hot and allowed to cool during 15 hours from 90° to room temperature in a flask well-lagged with cotton-wool. The precipitated amylose–butanol complex was separated at the centrifuge and the residue washed three times with cold butanol-saturated water. Two further similar reprecipitations involving six washings yielded a pale brown micro-spherocrystalline product (Schoch, *loc. cit.*). The amylose–butanol complex was decomposed by addition of water (40 c.c.) and removal of the butanol at 35°/15 mm. The residual aqueous solution was made up to 50 c.c. with water. The amylose content (0·1912 g., 55%) of the resulting solution was determined by hydrolysis of an aliquot portion with sulphuric acid and estimation of the liberated glucose with Somogyi's copper reagent. The product was not actually isolated in the solid state because of the possibility of retrogradation. Appropriate volumes of the aqueous solution were therefore used for the determination of the following properties of the sample of elm sapwood amylose: $[\alpha]_D^{17}$ +194° (*c*, 0·52 in water); blue value, 1·22; iodine uptake (measured potentiometrically), 19·6%.

Acetylation of Elm Sapwood Starch.—The starch was prepared for acetylation in a manner similar to that described by Haworth, Hirst, and Webb (*J.*, 1928, 2681) for potato starch. The air-dried starch (0·75 g.) was made into a paste with hot water (40 c.c.). After cooling, the paste was poured with stirring into 95% alcohol (400 c.c.), and the precipitated starch collected at the centrifuge, washed well with alcohol, and dried *in vacuo* over calcium chloride, to give a fluffy, cream-coloured powder (0·65 g.). The product (0·62 g.) was mixed with glacial acetic acid (6·5 c.c.) through which chlorine gas had been bubbled for 30 seconds. The mixture was stirred for 30 minutes at 20°, and then acetic anhydride (22 c.c. containing an amount of sulphur dioxide roughly equivalent to the chlorine in the glacial acetic acid) was added. Stirring was continued at room temperature for 1 hour, after which the temperature was raised to 55°. After 2—3 hours at this temperature, the starch dissolved, leaving a very fine greenish-brown precipitate suspended in the medium. This was removed at the centrifuge and the clear, colourless supernatant liquid poured with stirring into ice-cold water (1 l.). The precipitated starch acetate was collected at the centrifuge, washed first with water until free from acid, then with alcohol and ether, and dried *in vacuo* over calcium chloride. The white product (0·91 g., 83%) had $[\alpha]_D^{17}$ +167° (*c*, 1·0 in chloroform), $\eta_{sp.}^{20}$ 0·32 (*c*, 0·47 in *m*-cresol) (Found: $CH_3{\cdot}CO$, 44·9. Calc. for $C_{18}H_{16}O_8$: $CH_3{\cdot}CO$, 44·8%). The acetate was completely and easily soluble in acetone and in chloroform and, on evaporation of the solutions, clear, fragile films were formed.

In a previous experiment, the acetate of oak sapwood starch was prepared after preliminary dispersion of the starch in pyridine as recommended by Pacsu and Mullen (*J. Amer. Chem. Soc.*, 1941, **63**, 1487). Acetylation was effected by treatment with acetic anhydride, and the product was isolated and dried as described above for elm sapwood starch acetate. The brown oak starch acetate thus prepared was insoluble in acetone, chloroform, and *m*-cresol, although in the presence of these solvents the solid swelled considerably to form gelatinous lumps. Because of the unsatisfactory nature of this product it was considered desirable for the acetylation of elm sapwood starch to use the more drastic method described above.

Direct Methylation of Granular Elm Sapwood Starch.—The wood starch was methylated under conditions similar to those used by Hirst and Young (*loc. cit.*) for rice starch. The granules (2·5 g. of actual starch) were made into a smooth cream with water (20 c.c.), and sodium hydroxide (14 c.c.; 30% by wt.) was added. The air in the flask was displaced by nitrogen, a steady stream of the gas being maintained throughout. Sodium hydroxide (56 c.c.; 30%) and methyl sulphate (28 c.c.) were then added gradually at room temperature with vigorous mechanical stirring. After 15 hours' stirring at room temperature the mixture was again treated with sodium hydroxide (70 c.c.; 30%) and methyl sulphate (28 c.c.). A tendency for the mixture to froth was prevented by the addition of decyl alcohol. After a further 15 hours' stirring at room temperature, acetone (50 c.c.) was added and the mixture was evaporated first on the steam-bath at atmospheric pressure and finally at 75°/400 mm. As the acetone evaporated the partly methylated starch separated on the surface of the alkaline solution as an insoluble, spongy mass. The brown liquid was siphoned from beneath the insoluble product and neutralized by the cautious addition of sulphuric acid (50%) with cooling in an ice-bath. The neutral solution was dialysed against running tap-water for 3 days and then evaporated under reduced pressure at 40° to 15—20 c.c. This somewhat viscous solution was added to the bulk of the partly methylated starch dissolved in acetone (30 c.c.), and the product remethylated by the gradual addition of sodium hydroxide (70 c.c.; 30%) and methyl sulphate (28 c.c.). After 15 hours' stirring, the product was isolated as

described above, except that the hot alkaline liquor separated from the insoluble partly methylated starch was discarded on this and subsequent occasions.

The methylation procedure was repeated a further 11 times, the last twice at 40°. The product finally isolated was washed 3 times with boiling water and then dissolved in acetone. The solution was separated from inorganic material at the centrifuge and evaporated to dryness under reduced pressure at 30—35°. The residue was taken up in chloroform (150 c.c.), and the solution filtered through a G.3 sintered-glass filter. The filtrate was evaporated to 80 c.c. and poured slowly with vigorous stirring into light petroleum (800 c.c.; b. p. 60—80°). A pale-yellow oil (2·86 g., 91%) separated which solidified overnight (Found: OMe, 42·9. Calc. for $C_9H_{16}O_5$: OMe, 45·6%).

Fractionation of the Methylated Starch.—The methylated starch (2·85 g.) was dissolved in chloroform (100 c.c.), and light petroleum (b. p. 40—60°) was slowly added with thorough mixing. After the addition of 600 c.c. of petroleum, a pale yellow oil (fraction I) separated which solidified after decantation of the supernatant liquid and the addition of fresh petroleum. The bulk of the methylated starch in solution was precipitated by the addition of a further 100 c.c. of light petroleum, to yield fraction II, a pale yellow oil which solidified similarly. Further slight precipitation occurred on the addition of more light petroleum to a total volume of 1 l. The oily precipitate was combined with the residue obtained on evaporation of the chloroform–light petroleum mixture to dryness. The product (fraction III; 0·08 g.) was discarded.

Fraction I (0·21 g.) (Found: OMe, 43·7%) had $[\alpha]_D^{17}$ +207° (*c*, 0·51 in chloroform), $\eta_{sp.}^{30}/c$ 3·26 (*c*, 0·41 in *m*-cresol), corresponding to an apparent *M* of 494,000 (see Hirst and Young, *J.*, 1939, 1475). Fraction II (2·48 g.) (Found: OMe, 44·1%) had $[\alpha]_D^{17}$ +208° (*c*, 0·88 in chloroform); $\eta_{sp.}^{30}/c$ 3·08 (*c*, 0·45 in *m*-cresol), corresponding to an apparent *M* of 465,000. Fraction I was not further investigated.

Hydrolysis of Methylated Elm Sapwood Starch and Separation of Methylated Glucoses.—(a) *By paper chromatography.* The methylated starch (fraction II; 52 mg.) was hydrolysed at 100° with methanolic hydrogen chloride (1 c.c.; 4%) for 6 hours. The resulting methylglycosides were hydrolysed at 100° with aqueous hydrochloric acid (5 c.c.; 4%) for 6 hours. The hydrolysate was neutralized with silver carbonate and filtered. Silver ions were removed from the filtrate with hydrogen sulphide. After further filtration, the solution was shaken alternately with Amberlite resins IR-100 and IR-4B, and then evaporated to dryness under reduced pressure at 40°. The residual syrup (43 mg.) was dissolved in water (0·1 c.c.), and the components of the syrup were separated on a paper chromatogram and quantitatively estimated (see following Table) by the method of Hirst, Hough, and Jones (*loc. cit.*). The method was modified slightly by conducting the alkaline hypoiodite oxidations of the methylated sugars in the presence of a sodium hydroxide–phosphate buffer (pH 11·4) (Ingles and Israel, *loc. cit.*) in place of the carbonate–bicarbonate buffer (pH 10·6). The qualitative paper chromatograms and the marginal strips of the quantitative chromatograms were developed with aniline oxalate. On the assumption that the methylated starch contained 20·5% of methylated amylose, the figures in the Table indicate that the ratio of non-terminal to terminal groups in the amylopectin component was 20 : 1.

Sugar indicated	Estimated R_G value		Sugar in mixture, % by wt.
2 : 3 : 4 : 6-Tetramethyl glucose	1·0		4·3
2 : 3 : 6-Trimethyl glucose	0·84		86·5
2 : 3-Dimethyl glucose	0·60	estimated together	9·3
2 : 6-Dimethyl glucose and/or 3 : 6-dimethyl glucose	0·53		
Monomethyl glucose	0·29		trace
Glucose	0·11		trace

(b) *On a cellulose column.* The methylated starch (fraction II; 2·17 g.) was boiled with methanolic hydrogen chloride (100 c.c.; 1%) for 7 hours, after which the solution was cooled and cautiously neutralized with silver carbonate. The mixture was filtered and the insoluble residue of silver salts washed well with hot dry methanol. The filtrate and washings were concentrated to a syrup (2·41 g., 96%) which was dried in a vacuum over phosphoric oxide. The syrupy methylglycosides were hydrolysed at 95—100° with hydrochloric acid (100 c.c.; 2%) for 14 hours. After cooling, the solution was neutralized with silver carbonate and filtered, and silver ions were removed with hydrogen sulphide. The solution was filtered through a layer of "Filter Cel" and concentrated under reduced pressure at 40° to a syrup (2·18 g., 92·3%) which partly crystallized during 2—3 days.

A column of powdered cellulose (67 × 2·2 cm.) was prepared and washed as described by Hough, Jones, and Wadman (*loc. cit.*). The solvent was a 1 : 1 mixture of purified light petroleum (b. p. 100—120°) and *n*-butanol, saturated with water. The mixture of methylated glucoses (2·18 g.) from the above hydrolysis was dissolved in this solvent (5 c.c.), and the solution added dropwise to the centre of the top of the column, each drop being allowed to soak in before the next was added. The column was eluted with the solvent, and the eluate was collected in the receiving tubes which were changed automatically at 12-minute intervals. 4—5 C.c. of the eluate were collected in each of 300 tubes. The contents of every tenth tube were concentrated in a glass dish over a water-bath, any residue was dissolved in acetone, and small portions of each solution transferred in chronological order to the starting-lines of paper chromatograms which were then developed in the usual manner. The distribution of the sugars in the tubes was thus determined. The residues in the glass dishes were returned quantitatively to the respective tubes.

Tubes 20—30 contained 2 : 3 : 4 : 6-tetramethyl glucose, and after a gap of 20 tubes, 2 : 3 : 6-trimethyl glucose appeared (50—90). A further gap of 10 tubes was followed by the appearance of an apparently homogeneous dimethyl glucose (100—130), then a mixture of dimethyl glucoses (130—160), followed by an apparently homogeneous dimethyl glucose (160—200). Tubes 200—300 contained no reducing sugars. The column was finally washed with water (500 c.c.), to yield traces of monomethyl glucose and glucose. The eluates were grouped appropriately and the solvent was removed at 35°/20 mm. The residues in each case were dissolved in water and filtered through "Filter Cel." The filtrates were treated with charcoal at 35° for 15 minutes and refiltered through "Filter Cel." The solutions were evaporated at 40°/20 mm. and the residual syrups dissolved in acetone and filtered to remove traces of waxy impurities. After the removal of acetone, the syrups were dried *in vacuo* over phosphoric oxide for several days. The following fractions were thus obtained: (1) tetramethyl glucose (0·1911 g.); (2) trimethyl glucose (1·8032 g.); (3) dimethyl glucose (0·0581 g.); (4) mixed dimethyl glucoses (0·0658 g.); (5) dimethyl glucose (0·0816 g.); (6) monomethyl glucose; and glucose (0·0195 g.).

Fraction (1). The syrup showed no tendency to crystallize during 2 weeks although examination on a paper chromatogram indicated the presence of one sugar only (R_G 1·0) which corresponded to an authentic sample of 2 : 3 : 4 : 6-tetramethyl glucose. Quantitative determination by hypoiodite oxidation indicated the presence of 0·0949 g. of tetramethyl glucose in the syrup, the remainder of the syrup being represented mainly by trimethyl methylglucoside. The methylglucosides in fraction (1) (0·1857 g.) were hydrolysed at 95—100° with hydrochloric acid (17 c.c.; 2%) for 10 hours. The products (0·162 g., 90%) were isolated as described previously for the bulk hydrolysis of the methylated starch. The hydrolysis products were separated by use of the apparatus, method, and solvents previously described. The eluate was collected in a total of 250 tubes, each containing 4—5 c.c. Tubes 20—40 contained tetramethyl glucose. A gap of 20 tubes was followed by the appearance of trimethyl glucose (60—160). Although the remaining tubes (160—250) appeared to contain no reducing sugars, their contents were combined and evaporated to dryness. The residue examined on a paper chromatogram, sprayed with aniline oxalate, provided two spots of roughly equal intensities corresponding with 2 : 3- and 3 : 6-dimethyl glucose. The column was washed with water (500 c.c.) and the eluate evaporated to dryness. No reducing sugars were detected when the residue was examined on a paper chromatogram.

The following fractions were isolated and dried as described previously: (1*a*) tetramethyl glucose (0·0885 g.); (1*b*) trimethyl glucose (0·0682 g.); (1*c*) dimethyl glucose (0·0051 g.).

Fraction (1*a*) (a syrup) crystallized almost completely after the removal of traces of solvent. Examination by paper chromatography indicated the presence of a single substance (R_G 1·0) which corresponded to tetramethyl glucopyranose. Hypoiodite oxidation indicated that the fraction was 97% pure. The crystals (0·0847 g.) were recrystallized twice from light petroleum (b. p. 40—60°) and recovered in the form of long needles (0·041 g.), m. p. 85—87°, not depressed on admixture with an authentic sample of tetramethyl glucopyranose, $[\alpha]_D^{17}$ +96° (initial), +83° at equilibrium (*c*, 0·2 in water) (Found: OMe, 51·9. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The total recovery from the hydrolysate of the methylated starch was 91·7 (±3·2) mg., corresponding to one non-reducing end-group in 20 ± 1 residues in the amylopectin component.

Fraction (1*b*) (a syrup) partly crystallized on drying. Paper chromatography indicated the presence of one reducing sugar only, corresponding to 2 : 3 : 6-trimethyl glucose. Hypoiodite oxidation indicated that the fraction was 94·8% pure, $[\alpha]_D^{18}$ +85° (initial), +67° at equilibrium (*c*, 0·5 in water) (Found: OMe, 39·2. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). Fraction (1*b*) (0·031 g.) was dissolved in methanolic hydrogen chloride (10 c.c.; 1%) at room temperature. The rotation of the solution in a 2-dm. polarimeter tube was observed at intervals: $[\alpha]_D^{17}$ +64° (initial), $[\alpha]_D^{17}$ −36° (8 hours, constant).

Fraction (2). This partly crystallized on drying. Paper chromatography indicated the presence of a single sugar corresponding to 2 : 3 : 6-trimethyl glucose. Hypoiodite oxidation indicated that the fraction was 93·5% pure. The crude material (53·5 mg.) was treated with hydrochloric acid (3 c.c.; 2%) at 95—100° for 8 hours. The solution was neutralized and evaporated to a syrup as previously described. Examination of the residue on a paper chromatogram revealed the presence of very faint traces of dimethyl glucoses along with 2 : 3 : 6-trimethyl glucose. Fraction (2) (1·6 g.) was recrystallized twice from dry ether and the sugar recovered in the form of fine needles (0·71 g.), m. p. 113—115° with previous softening, alone or on admixture with an authentic specimen of 2 : 3 : 6-trimethyl D-glucopyranose (Found: OMe, 41·2. Calc. for $C_9H_{18}O_6$: OMe, 41·9%), $[\alpha]_D^{19}$ +98° (initial), +68° at equilibrium (*c*, 1·0 in water), $[\alpha]_D^{17}$ +69° (initial), −42° (final, 14 hours) (*c*, 1·1 in 1% methanolic hydrogen chloride).

Fraction (3). This did not crystallize. Hypoiodite oxidation indicated that the syrup contained 95·6% of dimethyl glucose. The position and colour of the spot on a paper chromatogram sprayed with aniline oxalate corresponded to 2 : 3-dimethyl glucose.

Fraction (4). This did not crystallize. Analyses as in the preceding paragraph indicated 94·8% of dimethyl glucose, of which two were present. These were separated on a paper chromatogram. Analysis by the method of Hirst, Hough, and Jones (*loc. cit.*) indicated that fraction (4) consisted of 53% of 2 : 3-dimethyl glucose. The remainder was probably represented by 3 : 6- and/or 2 : 6-dimethyl glucoses.

Fraction (5). This did not crystallize. Analysis as above indicated 94·3% of dimethyl glucose and the presence of one sugar only, but it is possible that the syrup consisted of 3 : 6- and/or 2 : 6-dimethyl glucoses.

Fraction (6). A paper chromatogram, when sprayed with aniline oxalate, revealed the presence of glucose and another sugar (R_G 0·20) which corresponded to a monomethyl glucose and gave a

red-brown spot. 3-Methyl glucose (R_G 0·19), which gave a brown spot, was used as the "control" sugar.

Partial Demethylation of 2 : 3 : 4 : 6-*Tetramethyl and* 2 : 3 : 6-*Trimethyl Glucoses.*—Samples of the appropriate sugars (50 mg.) were treated first with methanolic hydrogen chloride (1·5 c.c.; 1%) at 100° for 7 hours and then with aqueous hydrochloric acid (4 c.c.; 2%) at 100° for 14 hours. The samples were thus subjected to slightly more drastic treatment than the methylated starch during hydrolysis. The products were isolated in the usual way and the components of each syrup separated on paper chromatograms and determined with buffered hypoiodite. The results are collected in the Table.

2 : 3 : 4 : 6-*Tetramethyl glucose*	0·01N-$Na_2S_2O_3$ (c.c.).	Methylated sugar, %
Tetramethyl glucose	2·248	98·3
Trimethyl glucose	0·041	1·7
2 : 3 : 6-*Trimethyl glucose*		
Trimethyl glucose	2·611	98·5
Dimethyl glucose	0·042	1·5

Solvent Extraction of Gallotannin from Granular Elm Sapwood Starch.—It was found, after initial failures to remove the gallotannin impurity from the granules by a variety of methods including solvent extraction using a wide range of solvents, that treatment with boiling 85% aqueous methanol (Schoch, *loc. cit.*) produced the desired effect. Four successive extractions of the granules (0·8 g.) for 4 hours each with fresh batches (50 c.c.) of this solvent removed 6·4% of solid material based on the weight of the air-dried granules. The extracted material in aqueous solution gave the following positive reactions for gallotannin: (*a*) the addition of neutral ferric chloride solution gave a greenish colour, (*b*) a brown colour developed immediately on addition of sodium hydroxide solution, (*c*) a sparse reddish precipitate in the 2 : 2′-dipyridyl test (Feigl, *Ind. Eng. Chem., Anal.*, 1946, **18**, 62).

The residual starch granules retained their buff colour. On hydrolysis with sulphuric acid, a sample of the granules yielded a flocculent, brown residue of lignin-like material which, after being washed and dried, was treated with periodate as described below.

Periodate Oxidation.—(a) *Granular elm sapwood starch extracted with* 85% *aqueous methanol.* The granules (0·3120 g., containing 0·2942 g. of starch and 0·0178 g. of lignin) were suspended in water (52·5 c.c.) containing potassium chloride (2·5 g.), and sodium metaperiodate solution (7·5 c.c.; 0·293M.) was added. The oxidation and subsequent titrations were conducted as prescribed by Halsall, Hirst, and Jones (*loc. cit.*) for the determination of formic acid liberated by periodate oxidation of starches. "Corrected" titres: 1·482 c.c. of 0·01N-sodium hydroxide (172 hours); 1·571 c.c. (192 hours); 1·75 c.c. (268 hours); 1·922 c.c. (314 hours). These correspond with the formation of 3·91 mg. of formic acid after oxidation for 150 hours.

(b) *Lignin isolated after hydrolysis of elm sapwood starch.* The lignin sample (0·0215 g.) was treated with periodate under conditions identical with those described above for the oxidation of granular elm sapwood starch. "Corrected" titres: 0·289 c.c. of 0·01N-sodium hydroxide (167 hours); 0·29 c.c. (185 hours); 0·33 c.c. (262 hours); 0·49 c.c. (424 hours). From the results of this experiment it may be calculated that the lignin-like impurity (0·0178 g.) present in the starch sample oxidized with periodate was responsible for the generation of acidic material equivalent to 0·64 mg. of formic acid after oxidation for 150 hours.

The combined results of periodate oxidation experiments (a) and (b) thus indicate that the amylopectin component of elm sapwood starch liberated 3·27 mg. of formic acid after oxidation for 150 hours. This corresponds to the formation of 1 mole of formic acid per 10 glucose residues in that component.

Some of the work upon which this paper is based formed part of the programme of the Forest Products Research Board and the authors are indebted to the Department of Scientific and Industrial Research for permission to communicate the results.

Thanks are expressed to the Commonwealth Scientific and Industrial Research Organization for a grant (J. L. F.) and to the Distillers Company Limited and Imperial Chemical Industries Limited for grants.

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[*Received, August 17th*, 1951.]

770. *Cyclisation of Acid Chlorides by Friedel–Crafts Reactions.*

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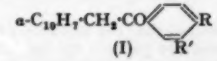
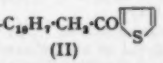
The Friedel–Crafts reaction of aluminium chloride upon various acid chlorides capable of undergoing cyclisation in the presence of molecules of various degrees of reactivity has been examined. The ease of formation of some five- and six-membered-ring ketones could thus be estimated from the extent of competitive formation of open-chain ketones; the results agreed with similar instances already recorded in the literature.

This work originated in an attempt to improve the preparation of acenaphthenone from 1-naphthylacetyl chloride (Friedlander, 1910/1912, **10**, 199; Buu-Hoï and Cagniant, *Compt. rend.*, 1942, **214**, 315) by replacing nitrobenzene and carbon disulphide by various aliphatic and aromatic compounds (including benzene) as solvents. Benzene had been found to be an effective solvent for the cyclisation, by the aid of aluminium chloride, of β-phenylpropionyl and γ-phenylbutyryl chlorides to indan-1-one and 1-tetralone (Amagat, *Bull. Soc. chim.*, 1927, **41**, 940); the same solvent had also been preferred for the cyclisation of γ-3-pyrenylbutyryl chloride (Vollmann, Becker, Corell, and Streeck, *Annalen*, 1937, **531**, 1). We have now found, however, that cyclisation of 1-naphthylacetyl chloride by means of aluminium chloride in benzene gave acenaphthen-1-one in very moderate yield, ω-1-naphthylacetophenone (I; R = R′ = H) being concurrently formed in large amount. When chlorobenzene was used as solvent, 4-chloro-ω-1′-naphthylacetophenone (I; R = Cl, R′ = H) was obtained in similar proportion. When the solvent was toluene, the main reaction product was 4-methyl-ω-1′-naphthylacetophenone (I; R = Me, R′ = H), and when the reaction was performed in carbon disulphide in the presence of thiophen, of anisole, and of veratrole, no acenaphthen-1-one was obtained, but only 2-1′-naphthylacetylthiophen (II), *p*-1′-naphthylacetylanisole (I; R = OMe, R′ = H), and 4-1′-naphthylacetylveratrole (I; R = R′ = OMe), respectively.



(I)



(II)

For the sake of comparison, this investigation was extended to β-phenylpropionyl chloride and its *p*-methyl and *p*-chloro-derivatives, and to γ-phenylbutyryl chloride. With β-phenylpropionyl chloride, our results were in agreement with Rothstein's observation (*J.*, 1951, 1459) that no open-chain ketone is obtained in benzene, whereas, in the presence of anisole, no indan-1-one is formed; we found that thiophen behaved like anisole, and 2-β-phenylpropionyl-

Table I.

Acid chloride	Aromatic or thiophen compound	Yield, %, of: cyclised product	Yield, %, of: open-chain ketone
β-Phenylpropionyl	Benzene	90	0
	Ethylbenzene	50	40
	Anisole	0	90
	Thiophen	0	80
	2 : 5-Dimethylthiophen	20	40
β-*p*-Tolylpropionyl	Benzene	95	0
	Ethylbenzene	50	40
	Diphenyl	90	0
	Chlorobenzene	70	0
	Anisole	0	90
	Thiophen	0	90
	2 : 5-Dimethylthiophen	15	40
β-*p*-Chlorophenylpropionyl	Benzene	0	70
	Ethylbenzene	0	80
	Diphenyl	0	80
	Anisole	0	90
	Thiophen	0	90
	2 : 5-Dimethylthiophen	0	60
γ-Phenylbutyryl	Benzene	95	0
	Ethylbenzene	70	20
	Chlorobenzene	80	0
	Anisole	0	80
	Thiophen	10	60
	2 : 5-Dimethylthiophen	20	30
1-Naphthylacetyl	Benzene	40	30
	Chlorobenzene	40	20
	Ethylbenzene	20	30
	Anisole	10	50
	o-Tolyl methyl ether	10	50
	Veratrole	10	60
	Thiophen	0	60
	2 : 5-Dimethylthiophen	0	50

thiophen was produced exclusively. Toluene in Rothstein's experiments took an intermediary position, as did ethylbenzene in ours. β-*p*-Tolylpropionyl chloride behaved substantially like its lower homologue, whereas β-*p*-chlorophenylpropionyl chloride was remarkably resistant to cyclisation, and yielded open-chain ketones exclusively, with benzene, ethylbenzene, diphenyl, thiophen, and anisole. A similar deactivating effect of nuclear chlorine atoms was observed by Kalinowski and Kalinowski (*J. Amer. Chem. Soc.*, 1948, **70**, 1970) in the cyclisation of *p*-chloro- and 2 : 4-dichloro-phenoxyacetic acid to the corresponding coumaranones. The outstanding susceptibility of γ-phenylbutyryl chloride towards cyclisation is demonstrated by the formation of 1-tetralone even in the presence of thiophen.

Table I, which gives the ratio of cyclised product to open-chain ketone (under our experimental conditions), not only expresses the ease of formation of cyclic ketones, but gives also a scale of the reactivity of various compounds in Friedel–Crafts ketone syntheses, which is similar to earlier results obtained by other methods.

The new ketones were characterised by Pfitzinger reactions with isatin, and by formation, from their phenylhydrazones, of generally well-crystallised 2 : 3-disubstituted indoles (cf. Buu-Hoï, *J.*, 1949, 2882).

Experimental.

Preparation of Intermediates.—1-Naphthylacetic acid free from its 2-isomer was best prepared from 1-methylnaphthalene by side-chain bromination with *N*-bromosuccinimide (Buu-Hoï, *Annalen*, 1944, **556**, 1), condensation with sodium cyanide, and hydrolysis of the nitrile obtained. The β-arylpropionic acids were prepared by standard malonate syntheses from the appropriate benzyl chlorides; γ-phenylbutyric acid was obtained from β-benzoylpropionic acid by means of a Kishner–Wolff reduction (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **67**, 2487). All the acid chlorides were prepared by the thionyl chloride procedure, and purified by vacuum-distillation.

Friedel–Crafts Reactions.—The aluminium chloride used was a pure product (Merck); the thiophen (Eastman Kodak), 2 : 5-dimethylthiophen (prepared from acetonylacetone and phosphorus trisulphide), benzene, ethylbenzene, and the phenyl ethers were redistilled and carefully dried.

(a) *With no extra solvent.* An ice-cooled solution of the appropriate acid chloride (1 part) in dry benzene, toluene, or chlorobenzene (5 parts) was treated with aluminium chloride in slight excess (1·2 mols. per mol. of acid chloride); the mixture was kept overnight at room temperature, and worked up in the usual way.

(b) *With an extra solvent.* The procedure was the same, except that the aromatic compound studied (1 part) was diluted in all instances with dry carbon disulphide (4 parts); the reaction mixture from thiophen and 2 : 5-dimethylthiophen, however, was kept at room temperature for only 2 hours.

Characterisation of Cyclisation Products.—Acenaphthen-1-one (b. p. 190—200°/16 mm.) was recrystallised from methanol and characterised by m. p. (120—121°) and mixed m. p., and by its oxime, m. p. 183°. Indan-1-one (b. p. 128—130°/12 mm.) was characterised by its m. p. (42°) and its semicarbazone, m. p. 236—238°. 6-Methylindan-1-one (b. p. 157—160°/18 mm.), recrystallised from methanol, had m. p. 62—63° (cf. Miller and Rohde, *Ber.*, 1890, **23**, 1898), and gave a *semicarbazone* crystallising from methanol in colourless needles, m. p. 256° (Found: C, 64·7; H, 6·2. $C_{11}H_{13}ON_3$ requires C, 65·0; H, 6·4%), and a *thiosemicarbazone*, forming from ethanol fine prisms, m. p. 220° (Found: C, 60·1; H, 6·0. $C_{11}H_{13}N_3S$ requires C, 60·3; H, 5·9%). 1-Tetralone was characterised by its semicarbazone, m. p. 223—225°.

In every instance, separation of the cyclic ketone from the far-higher-boiling open-chain ketone was satisfactorily achieved by vacuum-fractionation.

Pfitzinger Reactions.—A positive Pfitzinger reaction with isatin was observed with all the open-chain ketones obtained in the course of this work, except for 2 : 5-dimethyl-3-γ-phenylbutyrylthiophen, this failure being probably due to steric hindrance (cf. Buu-Hoï, *J.*, 1946, 795; 1948, 106) exerted by the methyl group in the *ortho*-position; some cinchoninic acids thus obtained, and their derivatives, are reported below. Except where other-wise stated the solvent for crystallisation was acetic acid.

3-1′-*Naphthyl*-2-*phenylcinchoninic Acid.*—A mixture of 1-naphthylacetylbenzene (2 g.), isatin (1·6 g.), and potassium hydroxide (1·8 g.) in ethanol (20 c.c.) was refluxed for 48 hours; after dilution with water and removal of the neutral impurities by ether-extraction, acidification with acetic acid yielded the *acid* as a yellow precipitate (0·8 g.) which formed from ethanol small crystals, m. p. 297° (decomp. above 270°) (Found: C, 83·0; H, 4·2. $C_{26}H_{17}O_2N$ requires C, 83·2; H, 4·5%).

3-*Benzyl*-2-p-*ethylphenylcinchoninic acid* formed colourless prisms, m. p. 296° (Found: C, 81·4; H, 5·9. $C_{25}H_{21}O_2N$ requires C, 81·7; H, 5·7%); its decarboxylation yielded 3-benzyl-2-*p*-ethylphenylquinoline, characterised by its *picrate*, forming from ethanol yellow needles, m. p. 217° (Found: N, 10·2. $C_{30}H_{24}O_7N_4$ requires N, 10·1%). 3-*Benzyl*-2-p-*methoxyphenylcinchoninic acid* formed colourless prisms, m. p. 271° (Found: C, 77·8; H, 5·2. $C_{24}H_{19}O_3N$ requires C, 78·0; H, 5·1%); 3-*benzyl*-2-p-*methoxyphenylquinoline picrate* formed from ethanol shiny yellow needles, m. p. 203° (Found: N, 9·8. $C_{29}H_{22}O_8N_4$ requires N, 10·1%).

2-p-*Methoxyphenyl*-3-p-*methylbenzylcinchoninic acid* crystallised in colourless prism, m. p. 276° (Found: C, 78·0; H, 5·4. $C_{25}H_{21}O_3N$ requires C, 78·3; H, 5·5%). 2-p-*Methoxyphenyl*-3-2′-*phenylethylcinchoninic acid* formed fine colourless needles, m. p. 278° (Found: C, 78·2; H, 5·2. $C_{25}H_{21}O_3N$ requires C, 78·3; H, 5·5%), and was decarboxylated to 2-4′-methoxyphenyl-3-2″-phenylethylquinoline whose *picrate* (from ethanol) had m. p. 206° (Found: N, 9·5. $C_{30}H_{24}O_8N_4$ requires

N, 9·8%). 3-p-*Chlorobenzyl-2-phenylcinchoninic acid* had m. p. 306° (Found: C, 73·6; H, 4·5. $C_{23}H_{16}O_2NCl$ requires C, 73·9; H, 4·3%); 3-p-*chlorobenzyl-2-phenylquinoline picrate* formed from ethanol shiny yellow prisms, m. p. 226° (Found: N, 9·8. $C_{30}H_{18}O_7N_4Cl$ requires N, 10·0%). 3-p-*Chlorobenzyl-2-p-ethylphenylcinchoninic acid* formed fine colourless needles, m. p. 261° (Found: C, 74·5; H, 5·0. $C_{25}H_{20}O_2NCl$ requires C, 74·7; H, 4·9%); 3-p-*chlorobenzyl-2-p-ethylphenylquinoline picrate* formed from benzene fine yellow prisms, m. p. 197° (Found: N, 9·2. $C_{30}H_{23}O_7N_4Cl$ requires N, 9·5%). 3-p-*Chlorobenzyl-2-p-methoxyphenylcinchoninic acid* formed fine colourless needles, m. p. 259° (Found: C, 71·0; H, 4·5. $C_{24}H_{18}O_3NCl$ requires C, 71·3; H, 4·4%). 3-p-*Chlorobenzyl-2-p-diphenylylcinchoninic acid* formed colourless prisms, m. p. 299° (Found: C, 77·2; H, 4·6. $C_{29}H_{20}O_2NCl$ requires C, 77·4; H, 4·4%); the picrate of its decarboxylation product had m. p. 204°. 3-2′-*Phenylethyl-2-2″-thienylcinchoninic acid* formed from methanol shiny colourless prisms, m. p. 242—243° (Found: C, 73·2; H, 4·5. $C_{23}H_{17}O_2NS$ requires C, 73·5; H, 4·7%); 3-2′-*phenylethyl-2-2″-thienylquinoline* crystallised from methanol in fine needles, m. p. 82° (Found: C, 79·8; H, 5·5. $C_{21}H_{17}NS$ requires C, 80·0; H, 5·4%).

Preparation of Indoles from Ketones Ar·$[CH_2]_n$·COAr′.—A solution of the crude phenylhydrazones of the ketones in acetic acid saturated with hydrogen chloride (cf. Buu-Hoï, *J.*, 1949, 2882) was brought to the boil, cooled, and poured into water; the indoles formed were taken up in benzene, and purified by vacuum-distillation and subsequent recrystallisation from methanol or ligroin. They all gave dark violet picrates. For these *ketones* and *indoles* see Tables II and III.

TABLE II.

Ketones of general formula Ar·$[CH_2]_n$·CO·Ar′.

Ketone *						Found, %:		Reqd., %:	
Ar	Ar′	*n*	M. p.†	B. p.	Formula	C	H	C	H
α-$C_{10}H_7$	C_6H_5	1	81°	250—255°/18 mm.	$C_{18}H_{14}O$	87·5	5·9	87·8	5·7
α-$C_{10}H_7$	*p*-C_6H_4Me	1	109	260—262/18	$C_{19}H_{16}O$	87·3	6·4	87·7	6·2
α-$C_{10}H_7$	*p*-C_6H_4Cl	1	97	260—265/18	$C_{18}H_{13}OCl$	77·1	4·8	77·0	4·6
α-$C_{10}H_7$	*p*-C_6H_4·OMe	1	124	260—265/18	$C_{19}H_{16}O_2$	82·3	6·1	82·6	5·8
α-$C_{10}H_7$	3 : 4-$C_6H_3(OMe)_2$	1	115	285—287/18	$C_{20}H_{18}O_2$	78·2	5·8	78·4	5·9
α-$C_{10}H_7$	2-C_4H_3S	1	82	260—262/18	$C_{16}H_{12}OS$	76·0	5·0	76·2	4·8
C_6H_5	*p*-C_6H_4Et	2	Liq.	232—235/18	$C_{17}H_{18}O$	85·4	7·7	85·7	7·6
C_6H_5	C_4H_3S	2	33	203—205/15	$C_{12}H_{12}OS$	72·0	5·8	72·2	5·5
C_6H_5	3-C_4HSMe_2- 2: 5	2	Liq.	209—210/15	$C_{15}H_{16}OS$	73·5	6·6	73·8	6·5
p-C_6H_4Me	*p*-C_6H_4Et	2	Liq.	244—246/18	$C_{18}H_{20}O$	85·8	8·1	85·7	7·9
p-C_6H_4Me	*p*-C_6H_4OMe	2	52	238—240/18	$C_{17}H_{18}O_2$	80·1	7·3	80·3	7·1
p-C_6H_4Me	2-C_4H_3S	2	Liq.	225—226/17	$C_{16}H_{16}OS$	73·2	6·0	73·0	6·1
p-C_6H_4Me	3-C_4HSMe_2-2 : 5	2	Liq.	217—219/14	$C_{18}H_{18}OS$	74·2	7·1	74·4	7·0
p-C_6H_4Cl	C_6H_5	2	58	230—232/18	$C_{15}H_{13}OCl$	73·3	5·1	73·6	5·3
p-C_6H_4Cl	*p*-C_6H_4Et	2	48	245/17	$C_{17}H_{17}OCl$	74·6	6·0	74·9	6·2
p-C_6H_4Cl	*p*-C_6H_4·OMe	2	78	258—260/16	$C_{16}H_{15}O_2Cl$	69·8	5·8	69·9	5·5
p-C_6H_4Cl	*p*-C_6H_4Ph	2	143	300—302/16	$C_{21}H_{17}OCl$	78·4	5·1	78·6	5·3
p-C_6H_4Cl	2-C_4H_3S	2	54	232—235/16	$C_{19}H_{11}OClS$	62·1	4·4	62·3	4·4
C_6H_5	*p*-C_6H_4Et	3	Liq.	244—245/18	$C_{18}H_{20}O$	85·6	8·1	85·7	7·9
C_6H_5	*p*-C_6H_4·OMe	3	56	240—242/18	$C_{17}H_{18}O_2$	80·0	7·0	80·3	7·1
C_6H_5	2-C_4H_3S	3	Liq.	205—207/14	$C_{14}H_{14}OS$	72·8	6·4	73·0	6·1
C_6H_5	2-C_4HSMe_2	3	Liq.	216—218/14	$C_{16}H_{16}OS$	74·2	7·2	74·4	7·0
C_6H_5	3 : 4-$C_6H_3(OMe)_2$	3	64	260/18	$C_{19}H_{20}O_3$	75·8	7·3	76·0	7·0

* The first six ketones crystallised from ethanol, and the other solid ketones from ligroin in colourless needles. All ketones gave yellow to orange halochromic colours with sulphuric acid.

† "Liq." denotes liquid.

TABLE III.

3- *and* 2 : 3-*Disubstituted indoles.*

	M. p.	Formula	Found, %: C	Found, %: H	Reqd., %: C	Reqd., %: H
3-β-Phenylpropionyl	161°	$C_{17}H_{15}ON$	81·6	6·2	81·9	6·0
2-Methyl-3-β-phenylpropionyl	147	$C_{18}H_{17}ON$	82·0	6·2	82·1	6·5
3-(β-*p*-Chlorophenylpropionyl)	198	$C_{17}H_{14}ONCl$	71·3	5·0	71·9	4·9
2-Methyl-3-(β-*p*-tolylpropionyl)	139	$C_{19}H_{19}ON$	82·2	7·0	82·3	6·8
3-(β-6-Tetralylpropionyl) *	150	$C_{21}H_{21}ON$	83·0	6·8	83·2	6·9
3-(β-*p*-Chlorophenylpropionyl)-2-methyl	165	$C_{18}H_{16}ONCl$	72·6	5·2	72·6	5·4
2-Methyl-3-γ-phenylbutyryl	158	$C_{19}H_{19}ON$	82·0	6·6	82·3	6·8
3-Benzyl-2-*p*-methoxyphenyl	152	$C_{22}H_{19}ON$	84·2	6·0	84·3	6·1
3-*p*-Chlorobenzyl-2-*p*-methoxyphenyl	166	$C_{22}H_{18}ONCl$	75·6	5·1	76·0	5·2
3-*p*-Chlorobenzyl-2-phenyl	111	$C_{21}H_{16}NCl$	79·2	5·2	79·4	5·0
3-*p*-Chlorobenzyl-2-*p*-ethylphenyl	101	$C_{23}H_{22}NCl$	79·6	5·6	79·9	5·8
3-*p*-Chlorobenzyl-2-*p*-diphenylyl	292	$C_{27}H_{20}NCl$	82·0	4·9	82·3	5·1
2-Methoxyphenyl-3-2′-phenylethyl	110	$C_{23}H_{21}ON$	84·5	6·2	84·4	6·4
3-2′-Phenylethyl-2-2″-thienyl	98	$C_{20}H_{17}NS$	79·0	5·8	79·2	5·6

* The acid was prepared from 6-chloromethyltetralin by the routine malonate synthesis.

Oddo Reactions with the Acid Chlorides (cf. *Gazzetta*, 1910, **40**, [2], 353, and Table III).—To a Grignard reagent made from ethyl bromide and magnesium in ether, indole (or 2-methylindole) was added, and the mixture refluxed for 15 minutes on a water-bath and then cooled in ice; a solution in ether of the appropriate acid chloride was added in small portions, and the reaction mixture refluxed for a further 15 minutes, and decomposed with an aqueous solution of ammonium chloride. After evaporation of ether, the solid ketones obtained were recrystallised from methanol or ligroin, forming shiny, colourless prisms.

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771. *Polarographic Behaviour of Iodo-compounds. Part II.**

By (Mrs.) E. Gergely and T. Iredale.

The polarographic reduction potentials ($E_{\frac{1}{2}}$) of the iodobenzoic acids, iodoacetic acid, iodoanilines, and iodophenols in various media and buffers of controlled pH, have been investigated. All of these compounds have half-wave potentials dependent on pH, and tentative explanations have been given of their behaviour. The possible part played by hydrogen bonding in the *ortho*-derivatives has been indicated. The influence of iodine on the reduction potentials of nitro and other neighbouring groups in the benzene ring is discussed, as well as the relationship of $E_{\frac{1}{2}}$ to " positive halogen."

We recorded in a previous communication (*J.*, 1951, 13) * that organic iodine is reducible at the dropping-mercury cathode by two different mechanisms. The iodo-hydrocarbons give half-wave potentials independent of hydrogen-ion concentration, whilst the ionizable compounds, such as iodoacetic acid, the iodobenzoic acids, iodoanilines, and iodophenols, have values of $E_{\frac{1}{2}}$ dependent on pH. The shift of the half-wave potential with pH cannot be attributed to dissociation equilibrium only. The greater part of this paper is concerned with these pH-dependent reductions.

Results.

Iodobenzoic Acids.—*o*-Iodobenzoic acid when reduced at a concentration of M/2500 in N/10-potassium chloride containing 5% ethanol gave a very wide wave from −1·00 to −1·70 v [all potentials are referred to the Standard Calomel Electrode (S.C.E.)]. When N/10-sodium hydroxide was added only one wave was obtained, having $E_{\frac{1}{2}} = -1{\cdot}6$ v. In weaker solutions (M/5000), however, two waves could be distinguished, the smaller one having $E_{\frac{1}{2}} = -1{\cdot}04$, the larger, $E_{\frac{1}{2}} = -1{\cdot}60$ v (Fig. 1). When reduction took place in M/100-tetraethylammonium bromide and 50% ethanol, two waves were again obtained, having $E_{\frac{1}{2}} = -1{\cdot}14$ and $-1{\cdot}60$ v. The first wave, however, was considerably higher than in the 5% ethanol plus potassium chloride supporting electrolyte. When the alcohol concentration was increased to 66%, the first wave continued to increase at the expense of the second wave. The sum total of both wave heights was constant, and therefore must be proportional to the total concentration of acid (Fig. 2). These experiments indicate, as Brdička (*Coll. Czech. Chem. Comm.*, 1947, **12**, 212) suggests for the reduction of pyruvic acid, that the first wave originates in the reduction of the undissociated acid molecules, the second wave in the reduction of the ions. This explains why increasing alcohol concentration augments the height of the first wave by shifting the dissociation equilibrium in the direction of the undissociated acid molecules. The wide wave obtained in potassium chloride solution could be explained by assuming that, after the reduction of the undissociated molecules present in the drop (electrode) area, the equilibrium is restored by recombination of hydrogen ions with acid anions. When reducing the *ortho*-acid in buffers, we could never obtain two waves in one polarogram, as in the acid buffers (pH 4—5) where the presence of both undissociated acid and ion is expected, the reduction of the ion is preceded by the decomposition of the buffer. The step heights of the waves obtained show that when the pH is less than 3 the acid is present largely in the associated state; from pH 3 to pH 5 the step-height decreases, showing that the measured wave is the reduction of undissociated acid only; in the range pH 5—7 the wave is probably due to reduction of both acid and ions; and when pH is greater than 9, the wave obtained is due to reduction of the ion only (Fig. 3). The half-wave potential of the undissociated acid appears, therefore, to shift with the pH, whereas that of the ion appears to be independent of pH.

The diffusion currents measured in acid media were about 15% larger than those measured in alkaline media. As the wave height does not decrease after the acid has been in alkaline buffers for a considerable time, this difference cannot be attributed to hydrolysis of the iodine to give the iodide ion.

m-Iodobenzoic acid was also reduced in one large step in N/10-potassium chloride or N/10-tetraethylammonium bromide and 5% ethanol. Separation of the two waves could not be achieved. In buffers the reduction follows a similar course to that of the *ortho*-acid.

p-Iodobenzoic acid was reduced in N/10-potassium chloride in a step which did not show double-wave character, the slope of the wave being the same as with the other iodo-compounds. In buffers

* Part I, *J.*, 1951, 13.

FIG. 1.

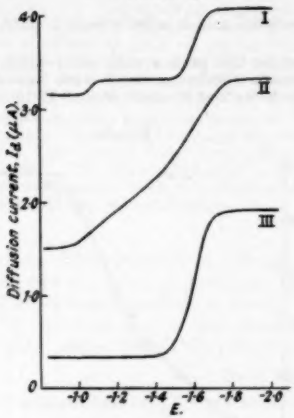


FIG. 2.

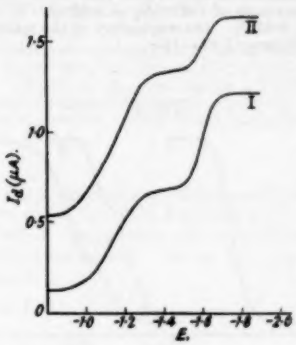


FIG. 1.

I. M/5000-o-*Iodobenzoic acid in* N/10-KCl–5% *ethanol.*
II. M/2500-o-*Iodobenzoic acid in* N/10-KCl–5% *ethanol.*
III. M/2600-o-*Iodobenzoic acid in* N/10-KCl–5% *ethanol and* N/100-NaOH.

FIG. 2.

I. M/3000-o-*Iodobenzoic acid in* M/100-*tetraethylammonium bromide*–50% *ethanol.*
II. M/3000-o-*Iodobenzoic acid in* M/100-*tetraethylammonium bromide*–66% *ethanol.*

FIG. 3.

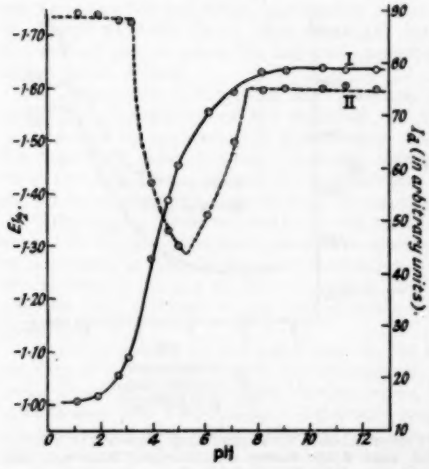


FIG. 4.

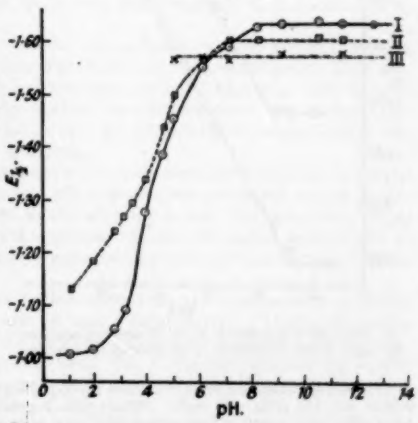


FIG. 3.

I. *Half-wave potential against* pH *for* o-*iodobenzoic acid.*
II. *Diffusion current of the measurable step.*

FIG. 4.

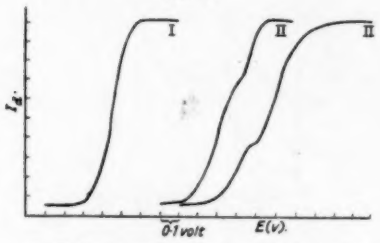
I. o-*Iodobenzoic acid.* II. m-*Iodobenzoic acid.* III. p-*Iodobenzoic acid*

the wave occurred only when the pH exceeded 5; as in the more acid regions the buffer decomposition preceded the reduction of the acid.

The order of increasing ease of reduction of the undissociated acid is *ortho* > *meta* > *para*, and of the acid anion *para* > *meta* > *ortho* (Fig. 4).

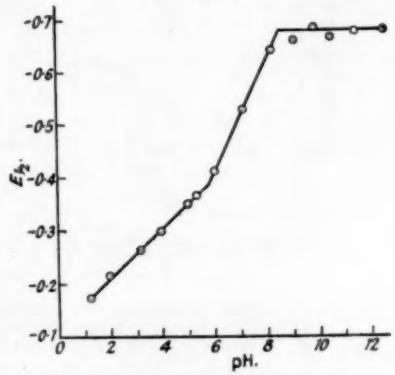
Iodoacetic Acid.—When reduced in N/10-potassium chloride this gave a wide wave which spread over a range of 0·5 v ($E_{\frac{1}{4}} = 0{\cdot}32$ v). If the solution was made alkaline, a usual wave was obtained ($E_{\frac{1}{4}} = 0{\cdot}65$ v). Determination of the value of $E_{\frac{1}{4}}$ in buffers shows that it varies from 0·17 to 0·68 v in the pH range 1·12—12·5.

FIG. 5.



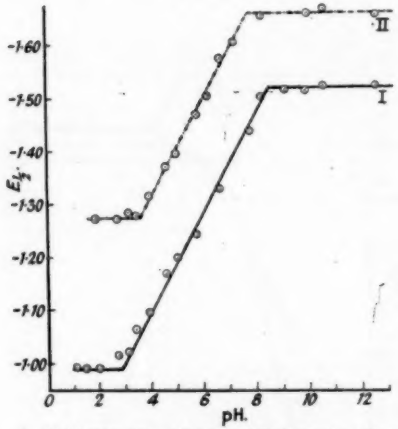
I. *Polarogram of iodoacetic acid in buffers of* pH < 6.
II. *Polarograms of iodoacetic acid in buffers of* pH > 6.

FIG. 6.



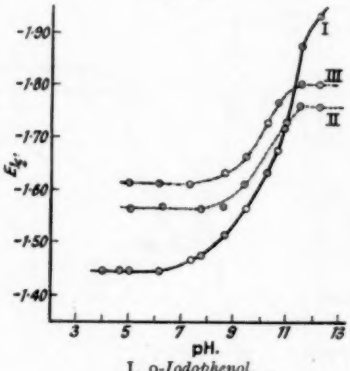
Plot of half-wave potential against pH *for* M/2500-*iodoacetic acid.*

FIG. 7.



I. *Half-wave potentials of* M/2500-o-*iodoaniline.*
II. *Half-wave potentials of* M/2500-p-*iodoaniline.*

FIG. 8.



I. o-*Iodophenol.*
II. m-*Iodophenol.*
III. p-*Iodophenol.*

The waves obtained in acid buffers up to pH 6 are the usual ones with logarithmic plots of the order of 0·08 v per log $i/(i_d - i)$ unit. When pH is greater than 6 the waves are extremely wide and are apparently composed of two waves with very poor separation (Fig. 5). The half-wave potential increases linearly with pH up to pH 5·5 with a slope of 0·045 v/pH, and above pH 5·5 the slope is more pronounced (0·085 v/pH). When pH > 9 the over-all half-wave potential does not change, but the double character of the waves is still observed (Fig. 6). The step-height corresponding to a two-electron reduction is in alkaline media about 5—10% lower than in acid media.

Iodoanilines.—In N/5-potassium chloride no sign of double-wave character was observed. The half-wave potentials in this medium are approximately equal to those in a buffer of pH 7. The horizontal lines obtained in the $E_{\frac{1}{4}}$/pH plot up to pH ~ 3 most probably represent the reduction of the

odoanilinium ion, and the horizontal lines in the alkaline region the reduction of the iodoaniline molecule (Fig. 7). The potential change in the intermediate pH region should be related in some way to the $IR{\cdot}NH_3^+ \rightleftharpoons IR{\cdot}NH_2 + H^+$ equilibrium. However, the relation is not very clear, as the waves obtained in buffers of pH 4—7 are narrow, and do not spread to either acid or alkaline potentials, and cannot be due to superposition of two waves. The diffusion currents measured were, within the experimental error, the same throughout the whole pH range. The iodoanilines, however, show maxima in the acid region, which are suppressed by addition of gelatin.

Iodophenols.—The reduction waves in N/5-potassium chloride are wide and might be composed of two elements. The straight line in Fig. 8 in the pH 4—7 region is the reduction of the iodophenol molecule. The upward trend from pH 8—12 is probably related to the equilibrium $IR{\cdot}OH \rightleftharpoons IR{\cdot}O^- + H^+$. The straight line at pH ~ 11—12 is probably the reduction of the iodophenoxide ion. The curve for *o*-iodophenol tends to a constant final potential, which, however, cannot be reached within the measurable pH and potential ranges.

Discussion.

General.—The reduction of iodo-compounds at the dropping-mercury cathode is a process requiring two electrons, as previously calculated with the aid of the Ilkovic equation (*J.*, 1951, 13). The reduction product is always the compound which results from the replacement of iodine by hydrogen, but it may arise from two different mechanisms. When the half-wave potential is independent of the pH the suggested mechanism is :

$$RI + 2e + H_2O = RH + I^- + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

When it is dependent on pH the mechanism may be :

$$RI + e + H^+ = RH^+ + I^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

followed by :

$$RH^+ + e = RH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Whether the two electrons add on at the same time or not cannot be decided from the $E_{\frac{1}{2}}$–log $i/(i_d - i)$ plot, this reduction being irreversible. The slopes of the logarithmic plots are of the order 0·09 v, which does not agree with the requirements for the reversible, one-electron process (0·06 v), or the two-electron process (0·03 v).

It is apparent that all the iodo-compounds having half-wave potentials dependent on pH contain groups undergoing electrolytic dissociation, whilst the pH-independent ones are non-electrolytes. Similarly it has been found that the double-bond of unsaturated hydrocarbons can be reduced at potentials independent of the pH (Laitinen and Wawzonek, *J. Amer. Chem. Soc.*, 1942, **64**, 1765, 2365; 1946, **68**, 2541), but in the case of the double-bond reduction of fumaric and maleic acids, the half-wave potential shifts with pH (Vopicka, *Coll. Czech. Chem. Comm.*, 1936, **8**, 349).

In attempting to attribute the half-wave potential dependence on pH entirely to the electrolytic dissociation of the molecule, we make the fairly obvious assumption that the reduction of the undissociated acid is easier and requires less potential than the reduction of the negatively charged anion, where the reducing electron has to overcome the electrostatic repulsion of the ion. It is to be expected also that the positively charged iodoanilinium ion should be more readily reduced than the neutral molecule.

If dissociation, however, were the only factor affecting the half-wave potential $E_{\frac{1}{2}}$, we should expect to obtain in the acid regions the more or less pH-independent reduction waves of the undissociated iodo-acids or iodoanilinium ion, and in the alkaline region, the reduction waves of the dissociated acid anions, or undissociated iodoanilines. In the pH region around pH = pK, we should expect to get two separate waves, each having pH-independent half-wave potentials.

In the extreme acid and alkali regions, the half-wave potentials are independent of pH in the case of *o*-iodobenzoic acid, the iodoanilines, and *m*- and *p*-iodophenols. If measurements could be carried out in the more alkaline region, the same results might be expected for *m*-iodobenzoic acid and *o*-iodophenol. Iodoacetic acid, however, has a pH-independent $E_{\frac{1}{2}}$ in the alkaline regions only, whilst in the acid regions a regular shift of 0·045 v per pH unit is observed. In the intermediate region two independent waves are not shown.

If the values of $E_{\frac{1}{2}}$ of the pH-independent compounds [iodobenzene, −1·62 v; *o*-, *m*-, and *p*-iodotoluene, −1·66, −1·61, −1·66 v, respectively (*J.*, 1951, 15); iodoethane, −1·67 v; iodomethane, −1·63 v (von Stackelberg and Strecke, *Z. Elektrochem.*, 1949, **53**, 118)] are compared with the values of $E_{\frac{1}{2}}$ of the pH-dependent compounds in acid buffers [*o*-iodobenzoic acid, −1·00 v; *o*-iodoaniline, −1·00 v; *m*-iodobenzoic acid, −1·13 v; *p*-iodoaniline, −1·28 v, etc.], it would seem that some interaction with hydrogen ions renders the reduction easier. In the alkaline buffers the $E_{\frac{1}{2}} \sim -1{\cdot}6$ v of all the pH-dependent compounds are of the same order as

those of the pH-independent compounds. There may be some balancing-out factor, which we have yet to discover, which makes the agreement fortuitous.*

For the iodoanilines, iodophenols, and iodoacetic acid at pH 5—8 we find $dE_{\frac{1}{2}}/dpH \sim 0{\cdot}085$—$0{\cdot}09$ v. According to von Stackelberg (*Z. Elektrochem.*, 1939, **45**, 466) for irreversible organic reductions where dissociation equilibria are involved :

$$dE_{\frac{1}{2}}/dpH = 0{\cdot}058(n_{ox.} - n_{red.})/v \text{ volts}$$

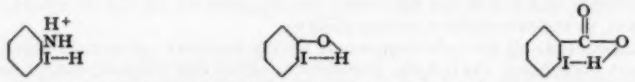
where v = number of electrons involved; $n_{ox.}$ = number of oxidized reactants; and $n_{red.}$ = number of reduced reactants.

Consider the reduction equation for an iodo-acid when pH > pK :

$$IR{\cdot}CO_2^- + 3H^+ + 2e \longrightarrow HR{\cdot}CO_2H + HI$$

here $n_{ox.}$ is 4 and $n_{red.}$ is 1; if it is assumed that hydrogen iodide does not affect the redox system the above equation beomes $dE_{\frac{1}{2}}/dpH = (4 - 1)0{\cdot}058/2 = 0{\cdot}087$ v/pH, which is in agreement with experiment.

In the alkaline regions the half-wave potential does not continue to move to more negative values with increasing pH, and the half-wave potentials are of the same order as those of the pH-independent reductions of iodo-hydrocarbons. When the hydrogen-ion concentration decreases to a limiting value, apparently mechanism (1), attributed to the pH-independent reductions, is the easier one. In the extreme acid regions with the iodophenols and iodoanilines (iodoanilinium ion), the hydrogen-ion concentration seems to be great enough to make the reduction potential independent of pH. It is, however, possible also that intramolecular hydrogen bonding might be a contributing factor, as the half-wave potentials of the *ortho*-derivatives are lower than those of the *para*-derivatives, although from electron-density considerations they might be expected to be approximately the same. The extremely low half-wave potential for iodoacetic acid, however, is not easy to explain on grounds similar to these.



Previous work has demonstrated the existence of hydrogen bonding in *ortho*-derivatives. In their investigation of the polarographic reduction of *o*- and *p*-nitrophenols, Astle and McConnell (*J. Amer. Chem. Soc.*, 1943, **65**, 35) attribute the lower half-wave potential of the *o*-compound to hydrogen bonding between the hydroxyl and the nitro-group. In their study of the electric moments of the *ortho*-halogenated phenols, Anziloth and Curran (*J. Amer. Chem. Soc.*, 1943, **65**, 620) conclude that 85—90% of the molecules have the hydroxyl group in the *cis*-position relative to halogen, owing to intramolecular bonding. The order of the bond strengths is H . . . . F > H . . . . . Cl > H . . . . . Br. The corresponding iodo-compound was not studied, but we may assume that some hydrogen bonding does exist in this case also. Some evidence of hydrogen bonding with iodine was also found from infra-red measurements on iodophenol (Wulf, Liddel, and Hendricks, *J. Amer. Chem. Soc.*, 1936, **58**, 2287).

The Influence of Iodine on Polarographic Reduction Potentials of Neighbouring Groups.—We reported in our previous paper (*J.*, 1951, 13) that the half-wave potential of combined iodine exhibits a shift to less negative potentials when electrophilic groups, and to more negative potentials when nucleophilic groups, are introduced into the same benzene ring; *e.g.*, the half-wave potential of undissociated *o*-iodobenzoic acid in tetraethylammonium bromide is $-1{\cdot}14_5$v, whilst that of *o*-iodotoluene is about $-1{\cdot}66$ v, of *p*-iodoaniline $-1{\cdot}72$ v, of *p*-iodophenol $-1{\cdot}71$ v, etc., the first being lower, the others higher, than the half-wave potential of unsubstituted iodobenzene, $-1{\cdot}62$ v, in the same medium. These results may be correlated with the Pauling–Wheland (*J. Amer. Chem. Soc.*, 1935, **57**, 2086) theory of electron densities, it being assumed that if the substituent causes by induction or resonance a greater electron density at the carbon atom where the iodine is bonded, the replacement of the iodine during the reduction will need more energy (greater negative potential) than that required for the reduction of iodobenzene, whilst if the substituent produces a lower electron density in the carbon–iodine region, the reduction will occur at a lower negative potential.

* This comparison is not made under quite the same conditions, as the $E_{\frac{1}{2}}$ values of the pH-independent compounds were measured in solutions containing 66% ethanol or 70% butanol, and would have approximately 0·06 v lower negative values in 5% ethanol solutions of which the buffers were made.

The halogens are electrophilic, but direct to *ortho* and *para* substitution. Iodine, as well as the other halogens, usually causes "red shift" in the absorption spectra of aromatic compounds, and behaves as "positive halogen" in certain organic reactions, especially if attached to a double-bonded carbon atom (Robertson and Waters, *J.*, 1947, 492; Atherton and Todd, *J.*, 1947, 674; Muirhead, *Annals App. Biol.*, 1949, **36**, 250). Our investigations with the iodonitrobenzenes and tetraiodopyrrole seem to agree with these facts. We have reduced these compounds at the dropping cathode in solution in M/100-tetraethylammonium bromide and 66% ethanol at a concentration of 1/3 millimol./l. Nitrobenzene gives one wave in this medium due to the reduction of the nitro-group. The iodonitrobenzenes give two waves, the first due to the reduction of the nitro-group, the second to replacement of the iodine :

Compound.	$E_{\frac{1}{2}}$ for the nitro-group.
Nitrobenzene	−0·935 v
o-Iodo-nitrobenzene	−0·816
m- ,,	−0·757
p- ,,	−0·780

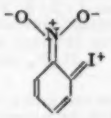
Tetraiodopyrrole is reduced in four steps; the $E_{\frac{1}{2}}$ for iodine of each step being : first step −0·74 v, second −0·90 v, third −1·10 v, fourth −1·60 v (there was poor separation for first three steps). The reduction potential of the monoiodopyrrole (−1·60 v) is thus of the order of the reduction potential of iodobenzene (−1·62 v).

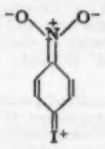
The comparative ease of the first reduction (−0·74 v) indicates the positive nature of the iodine when four iodine atoms are attached directly to the ring.

These results show that the presence of iodine attached directly to the ring enhances the reduction of the other reducible group, whether it is a nitro-group or another iodine. The order of increasing ease of reduction is :

m- > *p*- > *o*-iodonitrobenzene > nitrobenzene.

The iodine lowers the reduction potential of the nitro-groups in all positions in the ring because of its electron-attracting character. The electron deficiency all around the ring seems to be partly counterbalanced by a contribution of resonance structures such as those shown :





affecting only the *ortho*- and the *para*-positions. The lowest reduction potential for the *meta*-derivative is thus understandable.

It is interesting to compare these results with those obtained when chlorine is the modifying substituent. The following are the values of $E_{\frac{1}{2}}$ for the reduction of the nitro-group in the chloronitrobenzenes : *o*- −0·866 v, *m*- −0·830 v, *p*- −0·930 v.

The influence of chlorine is evidently less pronounced than that of iodine, and the order of increasing ease of reduction is different : *m*- > *o*- > *p*-chloro-compound > nitrobenzene.

The influence of chlorine on the reduction potential of the iodo-group itself shows itself more strongly : *o*- −1·34 v, *m*- −1·45 v, *p*-chloroiodobenzene −1·54 v, all of which are less than the $E_{\frac{1}{2}}$ for iodobenzene (1·62 v).

These differences are connected in some quantitative way with the electron-density differences in the specific groups, and theoretical work is being undertaken to discover this relation.

Experimental.

Details of the experimental apparatus and technique were described previously (*J.*, 1951, 13). The dropping-potentials were checked with the aid of the third electrode described by Lingane and Kolthoff (*J. Amer. Chem. Soc.*, 1939, **61**, 825). Chemicals used, with the exception of iodopyrrole, were purified by the group of workers engaged on their spectroscopy. Details will appear in forthcoming publications. The tetraiodopyrrole used was a May and Baker product (Found : N, 2·8. Calc. : N, 2·5%).

We gratefully acknowledge financial assistance from the Commonwealth Science Grant to this University.

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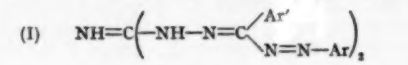
[*Received, June 21st*, 1951.]

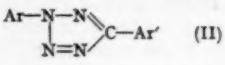
772. *A New Route to 2 : 5-Disubstituted Tetrazoles.*

By F. L. Scott, D. A. O'Sullivan, and J. Reilly.

As an introduction to a general investigation into the production of condensed heterocyclic compounds from the polyaminoguanidines, the oxidation of the " bisformazans " (I), from



(I)



(II)

diaminoguanidines, has been studied. Fission results, with the production of 2 : 5-disubstituted tetrazoles (II).

Experimental.—Microanalyses are by Drs. Weiler and Strauss, Oxford. All m. p.s are uncorrected.

Hydrazone formation. Typical examples are as follows :

Redistilled furfuraldehyde (11 ml.; an excess) was added to a concentrated aqueous solution of diaminoguanidine nitrate (7·1 g., 1 mol.); the resulting deep-brown solution on cooling deposited whitish-yellow needles of NN'-*bisfurfurylideneaminoguanidine nitrate*, which after recrystallisation from aqueous ethanol, melted at 121—122° (Found : C, 40·8; H, 4·5; N, 25·2. $C_{11}H_{12}N_4O_3,H_2O$ requires C, 40·5; H, 4·3; N, 25·8%). This hydrazone, which readily discoloured on exposure to light, forms a picrate, m. p. 253°.

When equimolecular quantities of *m*-nitrobenzaldehyde and diaminoguanidine nitrate are similarly mixed, a quantitative precipitation of NN'-*bis*-m-*nitrobenzylideneaminoguanidine nitrate* results. This compound, after recrystallisation from aqueous ethanol in which it was very sparingly soluble, melted at 250—252° (Found : C, 41·2; H, 3·9; N, 24·4. $C_{15}H_{14}O_7N_8,H_2O$ requires C, 41·3; H, 3·7; N, 24·5%). Recrystallisation from pyridine affords the anhydrous material (Found : C, 43·9; H, 3·6; N, 27·8. $C_{15}H_{14}O_7N_8$ requires C, 43·1; H, 3·4; N, 26·8%).

" Bisformazan " formation. *NN'*-Bisbenzylideneaminoguanidine hydrochloride (1·06 g., 1 mol.) was suspended in ethanol (95%) and an excess of concentrated potassium hydroxide solution added. The suspension was cooled to below 10°, the mixture well-stirred mechanically, and the calculated quantity of benzenediazonium chloride (2 mols.) was added. A deep purple colour immediately developed and the solution was set aside in an ice–salt mixture overnight. *Formimidobis-3 : 5-diphenylformazan* (*6-imino-1 : 3 : 9 : 11-tetraphenyl-3 : 6 : 9-tricarbaundeca-as-1 : 3 : 8 : 10-tetraenes* *) separated as a deep-red solid which was extremely soluble in the usual organic solvents and was purified by repeated boiling with water in which it was insoluble. It was thus obtained as a fine red amorphous powder, m. p. 137—138° (Found : C, 68·5; H, 5·15; N, 26·4. $C_{27}H_{22}N_8$ requires C, 68·5; H, 4·9; N, 26·6%).

When, similarly, diazotized potassium sulphanilate (2 mols.) was run into a well-agitated suspension of bisbenzylideneaminoguanidine nitrate (1 mol.) in excess of ethanolic potassium hydroxide solution (40%), the temperature being maintained below 10° during the addition, an analogous coupling results and during 24 hours, deep reddish-purple crystals of the *potassium 6-imino-3 : 9-diphenyl-3 : 6 : 9-tricarbaundeca-as-1 : 3 : 8 : 10-tetraene-1 : 11-disulphonate* separated (Found : C, 46·3; H, 2·6; N, 16·9. $C_{27}H_{21}O_6N_8S_2K_2$ requires C, 45·7; H, 3·0; N, 17·8%). The diacid was characterised as its p-*toluidine* salt, m. p. 227—229° (Found : C, 57·5; H, 4·9. $C_{41}H_{41}N_{11}O_6S_2$ requires C, 58·1; H, 4·8%).

When a solution of benzenediazonium chloride was treated in an analogous fashion with an aqueous ethanolic suspension of bis-*m*-nitrobenzylideneaminoguanidine hydrochloride in a strongly alkaline medium no coupling resulted. *6-Imino-3 : 9-di*-m-*nitrophenyl-1 : 11-diphenyl-3 : 6 : 9-tricarbaundeca-as-1 : 3 : 8 : 10-tetraene* was obtained however in the following fashion. A solution of benzenediazonium chloride was neutralized with solid sodium carbonate and then added to a solution of the hydrazone (1 mol.) in pyridine, the temperature being kept below 10° during the addition and with constant agitation; a deep red colour immediately developed and the addition of water precipitated the desired formazan as a dark-red amorphous material which after repeated extraction with boiling water had m. p. 148—149° (Found : C, 57·4; H, 4·1; N, 28·0. $C_{27}H_{21}O_4N_{11}$ requires C, 57·5; H, 3·7; N, 27·4%).

Oxidation of the formazans. Oxidation of the tetraphenyl compound with either lead tetra-acetate or nitrous oxide in anhydrous chloroform solution resulted in the production of 2 : 5-diphenyltetrazole, m. p. 101° (Dimroth and Merzbacher, *Ber.*, 1907, **40**, 2402, reported m. p. 102°) (Found : C, 70·2; H, 4·55; N, 24·4. Calc. for $C_{13}H_{10}N_4$: C, 70·3; H, 4·5; N, 25·2%).

Oxidation of both the tetraphenyl compound and the di-*m*-nitrophenyldiphenyl analogue with nitric acid resulted again in the production of tetrazole, with two nitro-groups substituted in the aryl residues. The orientation of the isomeric materials from these experiments is at present under consideration.

University College, Cork. [*Received, June 5th*, 1951.]

* The nomenclature is based on the use of " carba " to indicate replacement, by CH or CH_2 as appropriate, of one of a chain of hetero-atoms; in this case replacement by CH of one of a chain of nitrogen atoms, named in accordance with I.U.P.A.C. rule 43 f.

773. *Diglycine Hydrochloride.*

By Ronald Bentley.

In the preparation of isotopically labelled glycine ($H_2{}^{15}N{\cdot}CH_2{\cdot}CO_2H$) ethyl phthalimidoacetate is hydrolysed by concentrated hydrochloric acid (Schoenheimer and Ratner, *J. Biol. Chem.*, 1939, **127**, 301). After the removal of phthalic acid and evaporation of the solution to dryness, a residue of glycine hydrochloride is obtained. Free glycine is conveniently obtained by solution of the hydrochloride in ethanol and addition of pyridine. During one preparation of labelled glycine, a white crystalline solid, m. p. 182°, was obtained at this stage. It was shown qualitatively to contain chlorine and it seemed most likely that this compound was diglycine hydrochloride, $(H_2N{\cdot}CH_2{\cdot}CO_2H)_2{,}HCl$ (literature m. p. 186—187°). Since this was an isotopic preparation, the material was not further investigated; it was dissolved in aqueous ethanol and treated with more pyridine; glycine, m. p. 230°, was then obtained.

In further experiments with non-isotopic material, glycine was dissolved in concentrated hydrochloric acid and such solutions evaporated to dryness *in vacuo*. These preparations of glycine hydrochloride which must have contained a little free hydrochloric acid, were dissolved in ethanol and treated with an equimolar quantity of pyridine; diglycine hydrochloride, m. p. 185°, was regularly obtained. Use of a good excess of pyridine was necessary to precipitate free glycine.

Previously, diglycine hydrochloride had been prepared by the action of gaseous ammonia on an alcoholic solution of glycine hydrochloride (Kraut and Hartmann, *Annalen*, 1865, **133**, 101) and by reaction of glycine hydrochloride with glycine in boiling glacial acetic acid (Frost, *J. Amer. Chem. Soc.*, 1942, **64**, 1286).

Experimental.—Glycine (5 g.) was dissolved in concentrated hydrochloric acid (10 c.c.) with warming. The solution was evaporated to dryness *in vacuo*, and the residue further evaporated with ether (20 c.c.). The residue, which still contained free acid, was dissolved in warm ethanol (75 c.c.) and pyridine (5·5 c.c.) added with swirling. After 1 hour at 0° the white crystalline solid was filtered off; it had m. p. 186° (yield, 5·62 g.). When the compound was recrystallised from water by addition of ethanol its m. p. decreased to 181° [Found: N, 14·5. Calc. for $(C_2H_5O_2N)_2{,}HCl$: N, 15·0%].

National Institute for Medical Research, London, N.W.7. [*Received, August 1st*, 1951.]

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774. *The Mechanism of Amide Formation from Acids and Urea.*

By H. R. V. Arnstein and Ronald Bentley.

Cherbuliez and Landolt (*Helv. Chim. Acta*, 1946, **29**, 1438) have described a new general method for preparation of amides. When an acid was heated with urea, carbon dioxide and ammonia were evolved and the corresponding amide was obtained in good yield:

$$R{\cdot}CO_2H + H_2N{\cdot}CO{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}NH_2 + CO_2 + NH_3$$

Although it seemed likely that the reaction was the straightforward acidolysis postulated by Cherbuliez and Landolt, it was also possible that direct decarboxylation of the acid occurred, perhaps leading to a free radical, or that an intermediate $R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}NH_2$ decomposed with loss of the original carboxyl-carbon atom as carbon dioxide. In order to decide whether decarboxylation of the acid was involved, the reaction has been carried out with acids labelled in the carboxyl group with ^{13}C.

When $H{\cdot}{}^{13}CO_2H$ was used, the evolved carbon dioxide contained only the normal atom % of ^{13}C. The formamide produced was characterised as formylphenylhydrazide; after correction for the carbon of the phenyl group, this contained the same atom % excess ^{13}C as the formic acid. Similarly, with $CH_3{\cdot}{}^{13}CO_2H$, the evolved carbon dioxide had only the normal atom % of ^{13}C, and the acetamide isolated had the same atom % excess of ^{13}C as the acetic acid. It is clear therefore that all of the carbon dioxide produced in this reaction is derived from the urea.

The decomposition of urea oxalate (which yields carbon monoxide, carbon dioxide, ammonia, and cyanuric acid; Berzelius, "Lehrbuch der Chemie," 3rd edn., Dresden–Leipzig, 1840, vol. IX, p. 443) was also investigated, by use of urea oxalate prepared from ^{14}C-urea. Barium carbonate obtained from the carbon monoxide was not radioactive, indicating that the oxalic

acid moiety was the sole source of this product. The carbon dioxide produced in the reaction contained a substantial amount of ^{14}C, indicating that it was derived both from the oxalic acid and the urea.

Experimental.—[^{13}C]*Formic acid* (cf. Grant and Turner, *Nature*, 1950, **165**, 153). Potassium cyanide (1·252 g., 79·5% potassium cyanide, 56 atom % ^{13}C) in water (10 c.c.) was heated for 2 hours at 250° in a specially designed small autoclave (Kantorowicz, *J. Soc. Chem. Ind.*, 1950, **69**, Suppl. No. 2, S 76). After removal of a water-insoluble polymer (56 mg.) the solution was evaporated *in vacuo* (yield of crude potassium formate, 1·462 g.). Formic acid was steam-distilled after addition of excess of 2N-sulphuric acid, and the distillate treated with 1·01N-sodium hydroxide (16·9 c.c.). The solution was neutralised by addition of 6 c.c. of a solution of non-isotopic formic acid (= 52·92 mg. of formic acid). On evaporation *in vacuo*, 1·137 g. sodium formate were obtained.

Reaction of [^{13}C]*formic acid and urea.* Sodium [^{13}C]formate (10 mg., prepared as above) was refluxed briefly with anhydrous formic acid (0·2 c.c.) to effect the exchange reaction, $H\cdot{}^{13}CO_2Na + H\cdot CO_2H \rightleftharpoons H\cdot CO_2Na + H\cdot{}^{13}CO_2H$. The labelled formic acid was distilled in a closed vacuum system into a tube cooled in alcohol–carbon dioxide. The residual sodium formate was oxidised with van Slyke and Folch's chromic acid mixture (*J. Biol. Chem.*, 1940, **136**, 509); the carbon dioxide evolved was collected as barium carbonate which was treated with mineral acid in a special vacuum sample tube before analysis in a mass spectrometer (Arnstein and Bentley, *Quart. Reviews*, 1950, **4**, 174) (Found: atom % excess of ^{13}C, 1·17, 1·15).

The distillate ($H\cdot{}^{13}CO_2H$) was mixed with urea (0·23 g.) and heated in a stream of carbon dioxide-free nitrogen at 140—150° for 1½ hours. The carbon dioxide produced was absorbed in saturated barium hydroxide solution and analysed for ^{13}C in the usual way (Found: atom % excess of ^{13}C, 0·00, 0·00). The residue, consisting mainly of formamide, was distilled *in vacuo* (free flame) at water-pump pressure, to yield a viscous oil. For further purification, this product was warmed with an equal volume of phenylhydrazine at 135° until there was no further evolution of ammonia (15 minutes). A reddish crystalline solid was formed on storage overnight; it was washed first with water, then with 2N-hydrochloric acid, and recrystallised from a small volume of ethanol. The white plates, m. p. 144°, showed no m. p. depression on admixture with authentic formylphenylhydrazide (Found: atom % excess of ^{13}C, 0·16, 0·17. Hence, calc. atom % excess of original formamide = 1·16).

Reaction of [*carboxy*-^{13}C]*acetic acid with urea.* (*a*) Sodium [*carboxy*-^{13}C]acetate, $CH_3\cdot{}^{13}CO_2Na$, (50 mg., atom % excess of ^{13}C, 7·6; prepared at the Chemical Research Laboratory, Teddington) was dissolved, with warming, in glacial acetic acid (1 c.c.). The labelled acetic acid was then distilled off in a closed vacuum system (Found: atom % excess of ^{13}C, 0·20). The bulk of the acid was warmed with urea (1 g.) in a stream of carbon dioxide-free nitrogen at 110—120°. Evolution of carbon dioxide (which was collected as barium carbonate) took place slowly. After 20 minutes, carbon dioxide was collected for 30 minutes (Found: atom % excess of ^{13}C, 0·00). After a further 4 hours, a second sample of carbon dioxide was collected during 30 minutes (Found: atom % excess of ^{13}C, 0·00). (*b*) Sodium [*carboxy*-^{13}C]-acetate (10 mg., atom % excess of ^{13}C, 7·6) was equilibrated with glacial acetic acid (0·2 c.c.) as previously described. After distillation of the acetic acid, the residual sodium acetate was oxidised to carbon dioxide (Found: atom % excess of ^{13}C, 0·20, 0·20). The distilled [*carboxy*-^{13}C]acetic acid was warmed with urea (200 mg.) in a stream of carbon dioxide-free nitrogen at 185° for 3 hours. The residue was treated with saturated sodium hydrogen carbonate solution, a little insoluble material filtered off, and the solution extracted with chloroform (6 × 15 c.c.). The aqueous solution was evaporated to dryness *in vacuo* and the acetamide extracted from the residue with warm chloroform. The acetamide obtained on removal of solvent was oxidised to carbon dioxide (Found: atom % excess of ^{13}C, 0·22, 0·23).

Decomposition of [^{14}C]*urea oxalate.* The [^{14}C]urea oxalate was prepared by adding oxalic acid (624 mg.) to a solution of [^{14}C]urea (596·9 mg.) in water (6 c.c.). The product was crystallised from aqueous ethanol. This material gave 438·5 counts/min. when counted as a infinite thickness sample of 1 cm.² area on a thin-window bell-shaped Geiger–Müller counter (Popják, *Biochem. J.*, 1950, **46**, 560).

The above [^{14}C]urea oxalate was decomposed by heating it in a tube immersed in an oil-bath. A slow stream of dry carbon dioxide-free air was passed through the reaction tube; the exit gases were passed successively through three barium hydroxide traps to absorb carbon dioxide, a tube containing copper oxide heated to red heat, and a further three traps to absorp the carbon dioxide arising from the oxidation of carbon monoxide in the copper oxide tube.

The urea oxalate began to decompose at about 165° and the bath-temp. was kept at 170° till gas evolution ceased. The barium carbonate (224·7 mg.) arising from the carbon dioxide gave 197 counts/min. when counted in the same way as the starting material; the barium carbonate (95·7 mg.) derived from the carbon monoxide was completely non-radioactive.

We are indebted to the Chemical Research Laboratory, Teddington, for synthesis of the [*carboxy*-^{13}C]-acetate and to Mr. H. L. Kornberg for a gift of [^{14}C]urea.

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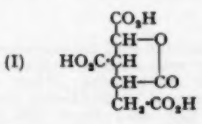
LONDON, N.W.7.

[*Received, August 17th*, 1951.]

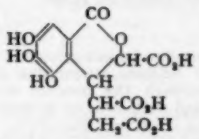
775. *Chebulinic Acid.*

By Robert D. Haworth and Leslie B. de Silva.

The work of Freudenberg and his collaborators (*Ber.*, 1919, **52**, 1238; 1920, **53**, 1728; *Annalen*, 1927, **452**, 303) indicated that chebulinic acid, the crystalline constituent of the fruits of *Terminalia chebula*, commonly called Myrobalans, had the molecular formula, $C_{41}H_{36}O_{27}$. Partial hydrolysis gave equimolecular proportions of gallic acid, 3 : 6-digalloyl glucose (see Schmidt and his co-workers, *Annalen*, 1951, **571**, 19, 29), and the so-called " split acid," which was isolated as the crystalline thallium and the brucine salt, gave a blue ferric test, and on pyrolysis yielded a small amount of pyrogallol. Later Schmidt and his colleagues (*Ber.*, 1947, **80**, 510; *Annalen*, 1951, **571**, 1) showed that " split acid," $C_{14}H_{12}O_{11}$, contains one lactonic, three hydroxyl, and three carboxyl groups, and methylation of the hydroxyl groups with diazomethane yielded the trimethyl derivative of " split acid," which gave a crystalline triamide. Oxidation of this trimethyl derivative with permanganate in acid solution gave a crystalline acid, $C_8H_8O_8$, containing one lactonic and three carboxyl groups, and structures (I) and (II) were suggested for this acid, $C_8H_8O_8$, and for " split acid," respectively, on the



(I)



(II)

following grounds. (i) The acid, $C_8H_8O_8$, resists decarboxylation; consequently it is not a malonic acid derivative, and the three carboxyl groups and the lactonic group are associated with different carbon atoms. (ii) The lactonic group is derived from a α-hydroxy-acid, because sodium cyanate was obtained by the action of sodium hypochlorite on the triamide of trimethyl-" split acid." (iii) The acid, $C_8H_8O_8$, yielded a mixture of acetic, oxalic, and succinic acids on fusion with potassium hydroxide, and oxalic acid on oxidation with alkaline permanganate. (iv) The formula proposed for " split acid " is attractive because (II) may be derived from ellagic acid by oxidative degradation of one of the phenolic rings.

It was assumed that the aromatic ring of (II) was destroyed during the formation of (I), but on the basis of formula (II) it would be expected that oxidation of the trimethyl derivative of " split acid " under appropriate conditions would give 3 : 4 : 5-trimethoxyphthalic acid. In our hands oxalic acid was the only product of the oxidation of the trimethyl derivative with alkaline permanganate, but welcome support of the suggestion of the aromatic nucleus has been obtained by the isolation of 3 : 4 : 5-trimethoxyphthalic acid, in yields exceeding 40% by the action of alkaline potassium ferricyanide on the trimethyl derivative of " split acid."

Experimental.—Potassium hydroxide (35 g.) was added to a solution of the trimethyl derivative of " split acid " (1 g.) in water (1·5 l.), and after the temperature had been raised to 80—90°, potassium ferricyanide (200 g.) was added with stirring. Further quantities of potassium ferricyanide (200 g.) and potassium hydroxide (35 g.) were added at the end of 12, 24, and 36 hours, and the stirred solution was maintained at 80—90° for 72 hours.

The solution was cooled, and the yellow crystals were collected and washed thoroughly with cold water. The combined filtrate and washings (1·5 l.) were acidified with dilute sulphuric acid and heated for several hours on a steam-bath to remove hydrogen cyanide, and the blue acidified solution was saturated with ether and allowed to cool in the refrigerator for 24 hours. The precipitated Prussian-blue was removed and the filtrate and the precipitate were continously extracted with ether during 48 hours. The ether was removed, the moist residue was evaporated under reduced pressure, and the yellow solid was sublimed twice at 140—150°/0·5 mm. Recrystallisation from ether gave 3 : 4 : 5-trimethoxyphthalic anhydride (256 mg.) as needles, m. p. 144° not depressed by admixture with an authentic specimen. Identity was confirmed by the preparation of *N*-methyl-3 : 4 : 5-trimethoxyphthalimide, m. p. 127° undepressed by admixture with an authentic specimen.

Our thanks are due to The Calder and Mersey Extract Company Ltd. for a supply of myrobalans, to the Government of Ceylon for a scholarship, and to Imperial Chemical Industries Limited for a grant.

The University, Sheffield, 10. [*Received, August 18th*, 1951.]

776. 2- *and* 5-*Fluoronicotinic Acids.*

By R. D. Beaty and W. K. R. Musgrave.

It has been reported (Hawkins and Roe, *J. Org. Chem.*, 1949, **14**, 328) that attempts to prepare 5-fluoronicotinic acid by a modified Schiemann reaction, the 5-amino-acid and ester being used as starting materials, failed because of the solubility of the diazonium fluoroborate. Eventually the required ester was prepared, *via* the diazonium silicofluoride, in approximately 15% crude yield. The preparation is now reported of methyl 5-fluoronicotinate, in a slightly lower yield than that from the diazonium silicofluoride, by the preparation and decomposition of the diazonium fluoroborate in fluoroboric acid; and also the preparation of 2-fluoronicotinic acid, in much better yield, by a similar procedure. The method of isolation of the 2-fluoronicotinic acid has been simplified, and this may be one reason for the increased yield, which in this case, is as good as that obtained in the preparation from 2-amino-3-methylpyridine (Minor, Hawkins, VanderWerf, and Roe, *J. Amer. Chem. Soc.*, 1949, **71**, 1125). Usually in the Schiemann reaction, the presence of a carboxyl group in the molecule greatly reduces the yield of fluorine-containing compound, when compared with that in the hydrocarbon reaction, but in this case the yields are about the same. Application of the process to the preparation of 3-fluoropicolinic acid from 3-aminopicolinic acid failed.

Experimental.

5-Fluoronicotinic Acid.—5-Aminonicotinic acid (3·0 g.) was dissolved in 40% fluoroboric acid (20 c.c.) and cooled to −5°. Sodium nitrite (2·5 g.) was added slowly with constant stirring, and after one hour in the ice-bath the product was heated to 50° for 30 minutes. When cooled, the solution was neutralised with sodium carbonate and the solvent removed by distillation under reduced pressure. After being dried *in vacuo* (P_2O_5) at 60°, the resulting salt was refluxed with 3% methyl-alcoholic sulphuric acid (50 c.c.) for 2—3 hours. The methanolic solution was filtered, neutralised with sodium methoxide, filtered again, and concentrated by distillation to about 2 c.c. On cooling, crystals of methyl 5-fluoronicotinate (0·3 g.), m. p. 48°, separated.

The methyl ester was dissolved in dry methyl alcohol (10 c.c.), and the solution saturated with ammonia at 0°. Next day the methyl alcohol was evaporated and the solid residue recrystallised from water, giving 5-fluoronicotinamide (0·2 g.), m. p. 174° (Found: F, 13·3. Calc. for $C_6H_5ON_2F$: F, 13·5%).

2-Fluoronicotinic Acid.—2-Aminonicotinic acid (2·0 g.) was dissolved in 40% fluoroboric acid (10 c.c.) and diazotised at 0° to −5° by the addition of aqueous sodium nitrite (1·0 g. in 10 c.c.). After 1 hour at 0° the solution was heated to 50—60° for a further hour. It was then cooled and basified to pH 5 by the addition of sodium hydroxide solution. The solid was filtered off and recrystallised from water, giving 2-fluoronicotinic acid (0·7 g., 33%), m. p. 164—165° (Found: F, 13·4. Calc. for $C_6H_4O_2NF$: F, 13·5%).

Esterification by refluxing the acid for 2 hours with 3% methanolic sulphuric acid followed by neutralisation of the solution with sodium methoxide, filtration, and evaporation to a small volume, gave, on cooling, crystals of the methyl ester, m. p. 74—75°.

The methyl ester (0·2 g.) was dissolved in absolute alcohol, saturated with ammonia at 0°, and set aside at 0° for one day. Evaporation of the solvent gave crystals of 2-fluoronicotinamide (0·16 g.) which, after recrystallisation from water, had m. p. 124° (Found: F, 13·4. Calc. for $C_6H_5ON_2F$: F, 13·5%).

One of us (R. D. B.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

The University, South Road, Durham. [*Received, August 22nd*, 1951.]

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777. *Fluorene-2-aldehyde.*

By S. J. Angyal, G. B. Barlin, and P. C. Wailes.

Two apparently different compounds have been described in the literature as fluorene-2-aldehyde. One was prepared by von Braun and Engel (*Ber.*, 1924, **57**, 191) by heating 2-bromomethylfluorene with hexamine in aqueous solution; they reported m. p. 174—175° for this compound and m. p. 245—247° for its semicarbazone. Hinkel, Ayling, and Beynon (*J.*, 1936, 339) prepared an aldehyde from fluorene by treating it with $AlCl_3$,HCN and hydrogen chloride; the position of the aldehyde group was established by reduction to 2-methylfluorene, and by oxidation to fluorene-2-carboxylic acid. This aldehyde melted at 90° and was characterised by its phenylhydrazone, oxime, anil, and semicarbazone (m. p. 278°).

In connection with our work on the Sommelet reaction, we have investigated von Braun's results by using the more readily prepared 2-aminomethylfluorene instead of the bromomethyl derivative. It has been established (Angyal, Morris, Tetaz, and Wilson, *J.*, 1950, 2141) that the use of an amine salt and hexamine in the Sommelet reaction is equivalent to the use of the addition compound made from a halogenomethyl compound and hexamine. When 2-aminomethylfluorene hydrochloride and hexamine were boiled in aqueous solution, a solid was formed, with a m. p. similar to that of von Braun's compound; but it was not an aldehyde. It contained nitrogen, and on acid hydrolysis it yielded 2-aminomethylfluorene and formaldehyde. Thus, von Braun's " aldehyde " is 2-methyleneaminomethylfluorene, a conclusion confirmed by its direct synthesis from the amine and formaldehyde.

A methyleneamine is always formed in the Sommelet reaction. In this case its low solubility in water prevented its further reaction. When the Sommelet reaction has been carried out in 50% acetic acid, which is a better solvent for the methyleneamine, the fluorenealdehyde described by Hinkel *et al.* has been obtained in 77% yield.

Experimental.—2-Aminomethylfluorene hydrochloride (von Braun and Engel, *loc. cit.*) was prepared in 81% yield by the hydrogenation of 2-cyanofluorene in the presence of Raney nickel at room temperature and atmospheric pressure.

2-Methyleneaminomethylfluorene. 2-Aminomethylfluorene hydrochloride (0·5 g.), hexamine (0·3 g.), formaldehyde (0·2 c.c., 40%), and water (7 c.c.) were boiled for 1 hour. During the whole time a solid was present which was filtered off (0·45 g.) and crystallised from ethanol; it then melted at 178°. When this compound was boiled with ethanol and concentrated hydrochloric acid (10 : 1) for 1½ hours, 2-aminomethylfluorene hydrochloride, m. p. 274°, crystallised on cooling, and from the mother-liquor formaldehyde was precipitated as its 2 : 4-dinitrophenylhydrazone, m. p. 160°. Both compounds were identified by their mixed m. p. with authentic samples.

A purer sample of *2-methyleneaminomethylfluorene* was obtained by dissolving 2-aminomethylfluorene hydrochloride (0·3 g.) in ethanol (15 c.c.; 65%), and adding sodium hydroxide solution (1 c.c.; 10%) and formaldehyde (1 c.c.; 40%). The precipitate was crystallised from much ethanol, or from pyridine–water, giving the fluorene, m. p. 181° (Found : N, 6·95. $C_{15}H_{13}N$ requires N, 6·75%).

When this Schiff's base was warmed with semicarbazide hydrochloride and sodium acetate in ethanol, a small amount of crystals, m. p. about 250°, was obtained. This was not a semicarbazone, however, but impure 2-aminomethylfluorene hydrochloride.

Fluorene-2-aldehyde. 2-Aminomethylfluorene hydrochloride (0·6 g.), hexamine (0·5 g.), and 50% acetic acid solution (6 c.c.) were boiled under reflux for ½ hour. After the addition of concentrated hydrochloric acid (0·5 c.c.) the mixture was cooled, diluted with water, and the precipitated aldehyde (0·39 g.) was collected and crystallised from dilute ethanol. The m. p., 85·5—86°, could not be raised by repeated crystallisation of the aldehyde from ethanol or from light petroleum, or by sublimation *in vacuo*. Hinkel *et al.* report m. p. 90°. In an attempt to purify the aldehyde further, it was converted into the anil, m. p. 159° (Hinkel *et al.* report m. p. 158°), and the anil was hydrolysed. When the anil (0·6 g.) was boiled with ethanol (10 c.c.) and concentrated hydrochloric acid (0·5 c.c.) for 1 minute, yellow crystals of the *anil hydrochloride*, m. p. 226—227° (0·4 g.), separated on cooling (Found : N, 4·8. $C_{20}H_{18}N,HCl$ requires N, 4·6%); but when the anil (0·5 g.) was boiled with ethanol (10 c.c.), water (5 c.c.), and concentrated hydrochloric acid (0·7 c.c.) for ½ hour, the aldehyde was obtained in nearly theoretical yield, but the m. p. was still 85·5—86°. The oxime, the phenylhydrazone, and the semicarbazone all had the m. p.s reported by Hinkel *et al.*

THE UNIVERSITY OF SYDNEY. [*Received, August 27th*, 1951.]

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778. *The Reaction of Sodiomalonic Ester with a Halogenocarboxylic Acid.*

By M. D. POTTER and E. P. TAYLOR.

THERE is apparently no reference in the literature to the reaction of sodiomalonic ester with a halogeno-compound containing a free carboxyl group. In cases where the product of such a reaction has been required, the carboxyl group has always been protected by esterification before treatment of the halogeno-compound with sodiomalonic ester. However, in one such case, conditions have now been developed for the direct condensation of the free acid with sodiomalonic ester.

Brassylic acid (undecane-1 : 11-dicarboxylic acid) has hitherto been prepared from 11-bromoundecanoic ester and sodiomalonic ester (see Chuit, *Helv. Chim. Acta*, 1926, **9**, 270). It has now been found that a much improved yield is obtained if the free 11-bromoundecanoic acid is used, provided that the quantity of sodiomalonic ester be increased. The results are

summarised in the table (the yields recorded are in each case the mean of at least two experiments).

Quantities of reactants			% yield of brassylic acid based on	
11-Bromoundecanoic acid (*a*) or ester (*b*) (mol.)	Sodium (mols.)	Malonic ester (mols.)	11-bromoundecanoic ester	11-bromoundecanoic acid
(*b*) 1	1·05	1·1	76	68·5
(*b*) 1	2·1	2·2	83	74
(*a*) 1	1·03	1·1	—	nil
(*a*) 1	2·06	2·2	—	53
(*a*) 1	3·09	3·3	—	87

It appears probable that the first mol. of sodiomalonic ester is immediately decomposed by the 11-bromoundecanoic acid to form the sodium salt, which then reacts with further quantities of sodiomalonic ester in the normal manner. In support of this, brassylic acid was obtained when equimolar quantities of sodiomalonic ester and sodium 11-bromoundecanoate were allowed to react, although the yield was poor (39%). In those experiments in which equimolar quantities of sodiomalonic ester and the acid were used, the crude product was not completely identified. Its melting point (approximately 56—60°) was higher than that of 11-bromoundecanoic acid. On fractional distillation of the derived methyl ester, a fraction was obtained corresponding in boiling point to methyl 11-hydroxyundecanoate, and which yielded 11-hydroxyundecanoic acid on hydrolysis (the melting point was unaltered on admixture with an authentic specimen). The presence of 11-hydroxyundecanoic acid in the reaction product may arise from the hydrolysis stage of the working up, since 11-bromoundecanoic acid readily yields the 11-hydroxy-acid in 92% yield when boiled with alkali.

Experimental.—Sodium (2·7 g., 3·09 mol.) was dissolved in dry absolute alcohol (60 ml.), and, with the temperature maintained at approximately 50°, ethyl malonate (19·8 g., 3·3 mol.) was run in with continuous stirring during 15 minutes. The solution was then refluxed and stirred whilst a solution of 11-bromoundecanoic acid (10 g., 1 mol.) (Ashton and Smith, *J.*, 1934, 435) in dry absolute alcohol (30 ml.) was added during 45 minutes. Stirring and refluxing were continued for another 30 minutes, water was added, and the alcohol was distilled off. The cooled solution was then made alkaline with sodium hydroxide, washed with ether, acidified with dilute hydrochloric acid, and extracted with ether. After removal of the solvent, the crude oily residue was refluxed with aqueous potassium hydroxide (22 g.; in 100 ml.) for 16 hours. The cooled mixture was then acidified, extracted with ether, dried (Na_2SO_4), and filtered, and the solvent removed. The residue was then partially decarboxylated by heating it at 170° for 70 minutes with gentle stirring. After cooling, the product was recrystallised once from dry benzene, whereupon 8·0 g. (87%) of brassylic acid, of m. p. 111° (uncorr.), were obtained.

We thank the Directors of Messrs. Allen and Hanburys Ltd. for permission to publish this note.

Research Division, Allen and Hanburys Ltd.,
Ware, Herts.

[*Received, September 19th*, 1951.]

THE CHEMICAL SOCIETY

SCIENTIFIC MEETINGS DURING JANUARY, 1952

LONDON.

Thursday, January 24th, 1952, at 7.30 p.m.

The "Gustav Tamann" Memorial Lecture, by Professor W. E. Garner, C.B.E., D.Sc., F.R.S.

ABERDEEN.

Friday, January 18th, 1952, at 7.30 p.m.

Lecture, **Recent Developments in Vitamin B_{12},** by Dr. T. F. Macrae, O.B.E., F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, Marischal College, Aberdeen.

BIRMINGHAM.

Friday, January 25th, 1952, at 4.30 p.m.

Lecture, **Chemistry of the Tropolones,** by Professor R. D. Haworth, D.Sc., F.R.S.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Edgbaston, Birmingham.

BRISTOL.

Thursday, January 24th, 1952, at 7 p.m.

Lecture and Demonstration, **High Vacuum in the Service of the Chemist,** by the Staff of W. Edwards and Co. (London), Ltd.

To be given in the Department of Chemistry, The University, Bristol.

EDINBURGH.

Thursday, January 17th, 1952, at 7.30 p.m.

Lecture and Demonstration by Quickfit and Quartz, Ltd.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held at the North British Station Hotel, Edinburgh.

EXETER.

Tuesday, January 22nd, 1952, at 5 p.m.

Lecture, **Inorganic Chromatography,** by Dr. F. H. Pollard.

Joint meeting with the Society of Chemical Industry to be held at Washington Singer Laboratories, Prince of Wales Road, Exeter.

GLASGOW.

Friday, January 18th, 1952, at 7.15 p.m.

Tilden Lecture, **The Contributions of Wave Mechanics to Chemistry,** by Professor C. A. Coulson, M.A., D.Sc., F.R.S.

To be given in the Chemistry Department, The University, Glasgow.

HULL.

Thursday, January 31st, 1952, at 6 p.m.

Lecture, **The Physics and Chemistry of Monolayers,** by Dr. J. H. Schulman.

To be given in the Science Lecture Theatre, University College, Hull.

IRISH REPUBLIC.

Wednesday, January 16th, 1952, at 7.45 p.m.

Lecture, **Recent Advances in the Chemistry of Algal Polysaccharides,** by Dr. F. J. Coll, M.Sc.

To be given in the Chemistry Department, Trinity College, Dublin.

LEEDS.

Monday, January 21st, 1952, at 6.30 p.m.

Royal Institute of Chemistry Lecture, **Recent Developments in Acetylene Chemistry,** by Professor E. R. H. Jones, D.Sc., F.R.S.

To be given in the Department of Chemistry, The University, Leeds. (All Fellows are invited.)

LIVERPOOL.

Thursday, January 24th, 1952, at 4.30 p.m.

Lecture, **Some Recent Advances in the Chemistry and Biochemistry of Porphyrins,** by Dr. A. Neuberger, F.R.S.

Joint meeting with the Royal Institute of Chemistry, the Society of Chemical Industry, and the British Association of Chemists, to be held in the Chemistry Lecture Theatre, The University, Liverpool.

MANCHESTER.

Thursday, January 17th, 1952, at 6.30 p.m.

Meeting for the Reading of Original Papers.

To be held in the College of Technology, Manchester.

(*NOTE.*—This meeting was originally arranged for January 24th.)

NEWCASTLE AND DURHAM.

Friday, January 25th, 1952, at 5.30 p.m.

Bedson Club Lecture, **The Contributions of Wave Mechanics to Chemistry,** by Professor C. A. Coulson, M.A., D.Sc., F.R.S.

To be given in the Chemistry Building, King's College, Newcastle. (All Fellows are invited.)

NORTH WALES.

Thursday, January 10th, 1952, at 5.45 p.m.

Lecture, **Mould Metabolic Products,** by Professor Alexander Robertson, M.A., Ph.D., F.R.S.

Joint meeting with the University College Chemical Society to be held in the Department of Chemistry, University College of North Wales, Bangor.

NORTHERN IRELAND.

Wednesday, January 30th, 1952, at 7.15 p.m.

Lecture, **Recent Research on the Control of Flowering Plants,** by Dr. Eric Ashby, D.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Lecture Theatre, Department of Agriculture, Queen's University, Belfast.

NOTTINGHAM.

Thursday, January 31st, 1952, at 4.45 p.m.

Lecture, **The Place of the Transuranic Elements in the Periodic Table,** by Dr. J. S. Anderson, M.Sc., A.R.C.S.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Nottingham.

ST. ANDREWS AND DUNDEE.

Friday, January 11th, 1952, at 5.15 p.m.

Lecture, **Isotopes in Biological Research,** by Dr. G. R. Tristram, B.Sc.

Joint meeting with St. Andrews University Chemical Society to be held in the Chemistry Department, United College, St. Andrews.

Thursday, January 17th, 1952, at 5.15 p.m.

Lecture, **Organic Fluorine Compounds,** by Professor M. Stacey, D.Sc., F.R.S.

To be held in the Chemistry Lecture Theatre, University College, Dundee.

Friday, January 25th, 1952, at 5.15 p.m.

Lecture, **New Approaches to the Study of Combustion,** by Professor R. G. W. Norrish, Sc.D., F.R.S.

Joint meeting with St. Andrews University Chemical Society to be held at the Chemistry Department, United College, St. Andrews.

Thursday, January 31st, 1952, at 5.15 p.m.

Lecture, **Some Recent Developments in Theoretical Organic Chemistry,** by Professor M. J. S. Dewar, M.A., D.Phil.

To be held at the Chemistry Lecture Theatre, University College, Dundee. (Arranged by the Chemistry Department and Fellows are invited.)

SHEFFIELD.

Thursday, January 31st, 1952, at 5.30 p.m.

Lecture, **Some Relations between Crystal Structures,** by Dr. A. F. Wells, M.A.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Sheffield.

PROCEEDINGS
OF THE
CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on November 1st, 1951, at 7.30 p.m.

PROFESSOR D. H. HEY, D.Sc., Ph.D., Vice-President, was in the Chair, and welcomed Professor H. T. Clarke (American Embassy), Professor O. Hassel (Oslo), and Professor Matsen (Texas), who were present.

MINUTES.

The Minutes of the Scientific Meeting held at Burlington House on October 18th, 1951, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: K. B. Bull, R. S. Cahn, A. Wasif.

SCIENTIFIC COMMUNICATIONS.

The following papers were read and discussed:

"The Relation between Configuration and Conjugation in Diphenyl Derivatives. Part I. The Optical Resolution and Ultra-violet Absorption Spectra of Some 2:2'-Bridged Compounds." By G. H. Beaven, D. Muriel Hall, Mary S. Lesslie, and E. E. Turner.

"Polyene Acids. Part II. The Stereochemistry of the β-Methylmuconic Acids." By J. A. Elvidge, R. P. Linstead, and P. Sims.

"Polyene Acids. Part III. A Re-investigation of Karrer's β-Methylmuconic Acid." By J. A. Elvidge, R. P. Linstead, and P. Sims.

"Structural Investigations of Co-enzyme A." By J. Baddiley and E. M. Thain.

Minutes of a

SCIENTIFIC MEETING

held in the Chemistry Department, University College, Swansea, on November 9th, 1951, at 5.30 p.m.

DR. L. E. SUTTON, M.A., F.R.S., Honorary Secretary, was in the Chair, and expressed the President's regrets at not being able to attend the first Official Meeting to be held in Swansea.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: T. C. James, R. H. Davies, B. G. Gowenlock, J. B. Bowen, A. J. Fudge, D. J. Jenkins, D. F. Williams, A. J. Owen, K. W. Sykes.

SCIENTIFIC COMMUNICATIONS.

The following papers were read and discussed:

"Ion-exchange Resins and Ester Hydrolysis." By G. G. Thomas and C. W. Davies.

"The Ionisation of Tri-*p*-tolylmethyl Chloride in Nitroalkanes." By A. Bentley and A. G. Evans.

"Steroids and Walden Inversion. Part VIII. Reactions of Some Steroid Grignard Compounds." By G. Roberts and C. W. Shoppee.

"The Reaction between Ferric and Iodide Ions. Part I. Kinetics and mechanism. Part II. The Influence of Ionic Association." By A. J. Fudge and K. W. Sykes.

At the conclusion of the meeting Dr. K. W. Sykes, Local Representative, expressed thanks to the Society for holding an Official Meeting in Swansea, and the Chairman, in reply, thanked the Department for hospitality and the speakers for their contributions to the meeting.

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on November 15th, 1951, at 7.30 p.m.

The President, SIR ERIC RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair, and welcomed Professor Mecke (Freiburg), who was present.

MINUTES.

The Minutes of the Scientific Meetings held in Burlington House on November 1st, 1951, and at University College, Swansea, on November 15th, 1951, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: D. J. Carr, B. Stevens.

SCIENTIFIC COMMUNICATIONS.

The following papers were read and discussed:

"The Photochemical Interaction of Anthracene and Alkyl Chlorides." By E. J. Bowen and Miss K. K. Rohatgi.

"The Photochemical Decomposition of Keten using Light of Very High Intensity." By K. Knox, R. G. W. Norrish, and G. Porter.

"Fluorescence from Formic Acid and Methylene Iodide." By P. J. Dyne, D. W. G. Style, and J. C. Ward.

Minutes of a

SCIENTIFIC MEETING

held in the Department of Chemistry, The University, Leeds, on Thursday, November 22nd, 1951, at 6.30 p.m.

Professor E. G. Cox, D.Sc., on behalf of the Vice-Chancellor of the University, extended a warm welcome to the Society, and the President, Sir Eric Rideal, M.B.E., M.A., D.Sc., F.R.S., who was in the Chair, replied on behalf of the Society.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: P. A. Briscoe, Edward R. Clark, Timothy L. Dawson, Edgar Collinson, E. J. Cross, R. A. Alderson, A. W. Walton, G. Youatt, G. M. Bristow, G. Hagues, G. L. Isles, M. O. Welch, J. Tiedt, Harry E. Nursten, E. N. White, R. E. Dean, E. J. Greenhow, A. W. D. Hartley, R. B. Hardwick, Felix Popper, W. L. Thomas, J. M. Landon.

TILDEN LECTURE.

After a brief introduction, the President called upon Professor D. H. Hey, D.Sc., F.R.I.C., to deliver the Tilden Lecture entitled "Some Recent Developments in the Chemistry of Free Radical Reactions in Solution." At the conclusion of the lecture, a vote of thanks to the Lecturer, proposed by Professor F. Challenger and seconded by Professor F. S. Dainton, was carried with acclamation.

OFFICIAL ANNOUNCEMENTS.

DEATHS.

The Council regrets to announce the deaths of the following Fellows:

	Elected.	Died.
Cyril Cuttell Howis (St. Helens)	Mar. 17th, 1949.	Sept. 21st, 1951.
William Dunlop McCreath (Bridgwater)	Dec. 7th, 1899.	Aug. 16th, 1951.
George Herbert Martin (Cheltenham) ...	June 16th, 1898.	Oct. 20th, 1951.
Thomas Chilwell Sharrott (Honiton) ...	Feb. 21st, 1895.	Sept. 15th, 1951.
Charles Kenneth Tinkler (Northwood) (C. 1930–33)	June 20th, 1907.	Oct. 25th, 1951.

MEDALS OF THE ROYAL SOCIETY.

Congratulations have been conveyed to the following Fellows on the award of Medals of the Royal Society:

Royal Medal: Sir Ian Heilbron.
Davy Medal: Sir Eric Rideal.

ELECTION OF NEW FELLOWS.

The following 27 Candidates were elected Fellows of the Society on November 15th, 1951.

Stuart Arnold Bellin.
Jack Gordon Bramley.
Ronald Frederick Branch.
John James Burton.
Kingsley Edward Calderbank.
Phillip Hugh Carter.
Erwin Chargaff.
Esmond Frank Collett.
Frank Colton.
Arthur Middleton Eastham.
Saiyid Ahmad Faseeh.
John George Fleetwood.
Lester Horwitz.
James Hugh Fraser Hurford.
Raymond Charles Isherwood.
John Alexander David Jeffreys.
Ian Moyle Lockhart.
John David McCollum.
Layton Leslie McCoy.
Frank Christopher Newman.
Clement Moxham Robertson.
Othmar Schindler.
Norman William Thomas.
Ramon Trujillo.
George Daniel Twigg.
Harry H. Wasserman.
Donald Sidney Withey.

VACANCIES ON COUNCIL.

In accordance with the Bye-Laws, the following vacant places on the Council fall due to be filled at the Annual General Meeting to be held in Dublin on Wednesday, April 16th, 1952:

Office.	*No. of Vacancies.*	*Names of Members who are due to retire.*
President	ONE	Sir Eric Rideal
Vice-Presidents who have filled the Office of President	ONE	Professor N. V. Sidgwick
Vice-Presidents who have not filled the Office of President	TWO	Professor J. W. Cook Professor W. Wardlaw
Elected Ordinary Members of Council:		
Constituency I (South-East England)	FOUR	Dr. R. Spence Dr. A. I. Vogel Dr. J. Walker Dr. W. A. Waters
Constituency II (Central and South-West England and South Wales)	ONE	Dr. S. J. Gregg
Constituency III (North-West England, North Wales and Isle of Man)	TWO	Professor C. E. H. Bawn Mr. J. D. Rose
Constituency V (Scotland)	ONE	Dr. N. Campbell

With the exception of Dr. N. Campbell and Dr. S. J. Gregg, who were appointed under Bye-Law 42, the members who are to retire are not eligible for re-election to the same Office until after a lapse of one year.

No vacancy arises for the Office of Honorary Secretary, or in Constituencies IV and VI.

In accordance with Bye-Law 23, the Council has nominated Professor C. K. Ingold to fill the vacancy in the Office of President. In accordance with Bye-Law 47, Sir Eric Rideal becomes a Vice-President who has filled the Office of President. Nominations by Fellows for the Offices of President and of Vice-President who has not filled the Office of President, should be made in writing and must be *signed by at least twenty Fellows.*

Fellows resident in a constituency may nominate any Fellow resident in that constituency for election to the Council to fill a vacancy among Elected Ordinary Members of Council allotted to that constituency. Every such nomination must be in writing *signed by at least fifteen Fellows resident in that constituency.*

Fellows may obtain forms of nomination from the General Secretary, and should state the vacancy for which they are requested. Every nomination must relate to one vacant place only, and must be accompanied by a signed declaration by the nominee that he is willing to accept office, if elected. Nominations must be received by the Society not later than Thursday, February 14th, 1952.

GIFTS OF PUBLICATIONS.

Acknowledgment is made of a gift of the Society's publications from Imperial Chemical Industries Limited, Dyestuffs Division.

LOCAL REPRESENTATIVE—LIVERPOOL.

The Council accepted with regret the resignation of Dr. W. B. Whalley as one of the Local Representatives for the Liverpool Area as from December 31st, 1951, and has appointed Dr. A. K. Holliday as his successor.

AMERICAN CHEMICAL SOCIETY—75th ANNIVERSARY CELEBRATIONS.

The following Address was presented on the occasion of the Seventy-Fifth Anniversary of the American Chemical Society at a ceremony in New York on September 5th, 1951 :

" THE CHEMICAL SOCIETY TO THE PRESIDENT, COUNCIL AND MEMBERS OF THE AMERICAN CHEMICAL SOCIETY

" We, the President, Council and Fellows of The Chemical Society, send you our fraternal greetings and warmest felicitations on the occasion of the celebration of the seventy-fifth anniversary of the foundation of the American Chemical Society.

" Since the meeting, called by your illustrious fellow-countryman, Professor Charles F. Chandler, and held in the City of New York on the Sixth Day of April 1876, at which your Society was founded, remarkable and significant progress has been made in chemical science in the New World. To this great advance, your Society has made a major contribution by the encouragement of research and development in all branches of Chemistry.

" We recall with satisfaction the many ties which, since the days of Joseph Priestley, unite the chemists of our two countries in the common pursuit of knowledge. During the past seventy-five years these bonds have been powerfully reinforced by the warm friendship between our Societies.

" We earnestly hope the American Chemical Society will continue to flourish and will contribute in ever-increasing measure to the advance of the science of Chemistry and to the well-being and the prosperity of mankind.

" Signed on behalf of the Chemical Society.

ERIC K. RIDEAL *President.*
W. A. AKERS *Treasurer.*
H. BURTON, E. D. HUGHES, L. E. SUTTON *Honorary Secretaries."*

London, 1951.

The following letter has been received from the American Chemical Society :

American Chemical Society,
1155, Sixteenth Street, N.W.,
Washington 6, D.C.,
October 18, 1951.

Sir Eric K. Rideal, President,
The Chemical Society,
Burlington House,
London, W.1, England.

" Dear Sir Eric :

" The striking address so beautifully bound in the colors of the American Chemical Society presented to us by The Chemical Society on the occasion of our Diamond Jubilee is one of the valued mementos of this event. The celebration has left happy memories in the minds of thousands. In the years to come re-examination of the addresses and gracious letters from our sister societies, presented at this time, will bring back these recollections.

" Yours is a memento which has particular value to us. It comes from our elder associate in the field of chemical organization, one which inspired our founders in 1876 and to which we always have looked as an elder brother. Your signature on the address and your participation in the ceremonies at which it was presented add to its value for us. We hope that you always will regard this country as a second home and trust that your visits in the future may be even more frequent than in the past.

" Our science is international in scope, and the activities of this Society extend far beyond the borders of the United States. For that reason, we felt that the celebration of our seventy-fifth birthday would not be complete if colleagues from all parts of the world did not have a part therein. Therefore, all of us were gratified that the society of which you are president could help us pay tribute to the past and launch us on an even more eventful future.

" It is my feeling that the event held in New York last month has drawn all of us closer together. We hope that those ties will continue and that they may be even firmer in the future. The American Chemical Society trusts that the coming years will witness increased international cooperation in the utilization of chemistry for the happiness, well-being, and prosperity of mankind.

Cordially yours.
(*signed*) N. H. FURMAN.
President."

NOMENCLATURE PROPOSALS.

Fellows wishing to submit extensive nomenclature proposals should send them to the Publication Committee for consideration. If adopted, the proposals would be published, with acknowledgments to the author, in the annual Editorial Report on Nomenclature.

NOMENCLATURE—I.U.P.A.C. COMMISSION.

The use of syllables ending in " a," such as oxa, aza, thia, etc., for indicating substitution by a hetero-atom into a ring skeleton has become well established; *e.g.*, a name such as 2 : 7 : 9-triazaphenanthrene is now generally understood. This usage is the subject of I.U.C. rule 16 (cf. *J.*, 1931, 1610). A more modern version of this rule was evolved by the Commission of Nomenclature of Organic Chemistry of the International Union of Pure and Applied Chemistry at its meetings in New York, in September, 1951, and will shortly be published on a tentative basis.

The new rule, like the present rule 16, is confined to heterocyclic systems. The Organic Commission also considered extension of this principle to aliphatic compounds in which the main chain of atoms contains a preponderance of hetero-atoms; for instance, the compound $HO{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}OH$ might be named 2 : 5-dioxahexane-1 : 6-diol; the compound $CH_3{\cdot}O{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ might be named 2 : 4 : 6-trioxanonan-

9-oic acid; the compound $H_2N{\cdot}CH_2{\cdot}NH{\cdot}NH{\cdot}CH_2{\cdot}NH{\cdot}NH{\cdot}NH_2$ might be named 2 : 5-dicarbaoctazane. However, several alternatives arose when details of the rule(s) necessary for aliphatic application were discussed, and the need was felt for as wide a knowledge as possible of actual compounds to which this nomenclature could usefully be applied.

The Commission would be grateful to be told of relevant examples; but it is emphasized that these should be compounds actually prepared (whether published or not) or in an advanced stage of preparation; purely theoretical compounds are not of interest as the desire is to discover the field of practical use to be covered.

Silicon compounds are excluded from this request as they are covered by I.U.P.A.C. rules 70.1 to 70.20.

Those (in Great Britain and kindred countries) who are willing to help are invited to send formulæ of relevant compounds to the Editor, The Chemical Society.

MEETINGS OUTSIDE LONDON

BIRMINGHAM.

"Some Aspects of Oxidation and Corrosion," by Dr. U. R. Evans, F.R.S.

A joint meeting with the University Chemical Society was held in the Chemistry Lecture Theatre of the University on October 26th, 1951, with Dr. L. L. Bircumshaw in the Chair.

Evidence—qualitative and quantitative—was presented for Wagner's view that the growth of oxide films at high temperatures (and of sulphide films at ordinary temperatures) proceeds by outward movement of cations and electrons through the films. Substances relatively impervious either to cations or to electrons produce protective films. Hence the resistance of materials containing aluminium, chromium, or silicon.

Zinc exposed to dry air takes up measurable quantities of oxygen, but sensitive spots in the film are soon reinforced and the action becomes so slow that there is no visible change. Likewise, zinc whirled in pure water containing oxygen suffers no visible change, but, if the water is stagnant, the oxygen replenishment rate is insufficient and cations enter the liquid; pitting then occurs at the sensitive spots. This anodic reaction is balanced electrically by a "cathodic reaction"—the reduction of oxygen to hydrogen peroxide or hydroxyl ions at an adjacent area. The electrochemical attack on zinc (or iron) can only be prevented by exceptional conditions, such as whirling (unless an inhibitor is added to make the entry of cations into the liquid impossible). Materials containing aluminium, chromium, or silicon, with protective films, can remain uncorroded in oxygen containing water, which is stagnant and contains no inhibitor.

EDINBURGH.

"Micro-photography—The Production of Minute Photographs," by Dr. G. W. W. Stevens.

A joint meeting with the Local Sections of the Royal Institute of Chemistry and the Society of Chemical Industry was held in the North British Station Hotel, Edinburgh, on Thursday, October 18th, 1951, with Mr. F. J. Bolton in the Chair.

After referring to the loss sustained by the death of Dr. E. G. V. Percival, the Chairman introduced the Lecturer, who gave a lucid account of the history, theory, and applications of the subject. A discussion followed, and the vote of thanks to the Lecturer, proposed by Dr. E. A. B. Birse, was carried with acclamation.

SHEFFIELD.

"Colour Photography," by Dr. H. Baines, F.R.I.C.

A joint meeting of the Chemical Society and the Royal Institute of Chemistry was held in the Chemistry Lecture Theatre on Thursday, October 11th, 1951, with Mr. H. C. Hillary, F.R.I.C., in the Chair.

Dr. Baines gave a clear explanation of the processes of colour photography which had been found to be of practical value, and his wide variety of illustrative slides gave much pleasure to his audience. On the motion of Dr. A. S. C. Lawrence, a cordial vote of thanks was given to the Lecturer.

" The Synthesis of Sugars," by Dr. J. K. N. Jones, M.Sc., A.R.I.C.

A joint meeting of the Chemical Society and the University Chemical Society was held in the Chemistry Lecture Theatre on Thursday, November 8th, 1951, with Professor R. D. Haworth, F.R.S., in the Chair.

Starting from Emil Fischer's synthesis of hexoses from " formose," Dr. Jones gave an interesting review of modern developments in this field, paying particular attention to the biochemical mechanisms which might give rise to the naturally occurring pentoses, hexoses, and heptoses. On the motion of Dr. J. McKenna, a cordial vote of thanks was given to the Lecturer.

SOUTHAMPTON.

" Nitration and Nitrating Agents," by Professor C. K. Ingold, D.Sc., F.R.S.

A joint meeting with the Portsmouth and District Chemical Society was held in the Municipal College, Portsmouth, on October 30th, 1951, with Mr. J. M. Wilson in the Chair.

Professor Ingold gave a most interesting account of the results of kinetic studies on aromatic nitration in non-aqueous media, and showed how these were explained by the action of the nitronium ion in the nitration process. A very full account of the physical evidence for the existence of the nitronium ion was given. The lecture was illustrated by slides, and specimens of several nitronium salts were shown.

After the discussion, a vote of thanks to Professor Ingold was proposed by Mr. E. A. S. Cavell, and carried enthusiastically by the large audience.

" The Chemistry of Co-enzyme A," by Dr. J. Baddiley.

A joint meeting with the Southampton University College Chemical Society was held in the Physics Department, University College, Southampton, on November 2nd, 1951, with Mr. E. A. S. Cavell in the Chair.

Dr. Baddiley considered first the nature and structure of pantothenic acid and mentioned the widespread occurrence of the substance in vital systems. He then gave a clear account, illustrated by slides, of the progress so far made in the elucidation of the chemical structure of the related co-enzyme A, and indicated possible solutions to structural problems which still remain. After a brisk discussion, a vote of thanks to Dr. Baddiley was proposed by Mr. C. W. Rees and carried with enthusiasm.

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objection to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the " Journal " for December, 1951. Such objections will be treated as confidential. The forms of application are available in the Library.)

***Anderson, Dennis.** British. The Bungalow, Mount Road, Wheathampstead, Nr. St. Albans, Herts. Assistant Organic Chemist, The Murphy Chemical Co., Ltd. *Signed by:* M. Pianka, J. L. Walpole, R. L. Collett.

Andrisano, Renato, D.Chem. (Ferrara). Italian. Istituto Chimica Farmaceutica, Universita Degli Studi, Catania, Italy. Professor of Pharmaceutical Chemistry. *Signed by:* C. K. Ingold, C. A. Bunton, B. Ross.

***Armstrong, Andrew Johnston.** British. 10, Adamton Terrace, Prestwick, Ayrshire. University Student. *Signed by:* J. C. Speakman, J. C. James, T. H. Goodwin.

***Baum, Harold,** B.Sc. (Birm.). British. 39, Sandon Road, Edgbaston, Birmingham 17. Chemical Research Student. *Signed by:* L. L. Bircumshaw, S. R. Carter, G. A. Gilbert.

Benkendorff, Gerhard Werner, D.Sc. (Berlin). German. 14, Malvern Road, Maidenhead, Berks. Chief Chemist with Tretol, Ltd. *Signed by:* L. J. Bellamy, C. G. Strain, E. W. S. Press.

***Betterton, Albert James.** British. 188, Botley Road, Oxford. Student. *Signed by:* L. A. Waters, Ivan M. Roitt, T. J. L. Aparicio.

***Bevan, David John Martin,** M.Sc. (Melbourne). British. 17, Hillside, A.E.R.E., Harwell, Berks. Harwell Research Fellow. *Signed by:* B. J. Roberts, R. W. M. D'Eye, J. Sutton.

***Blake, Peter Gerald.** British. 5, Goodall Road, Leytonstone, E.11. Laboratory Assistant, Lewis Berger Ltd., London, E.9. *Signed by:* H. Holness, K. R. Lawrence, A. P. MacKenzie.

***Bodger, Derek,** B.Sc. (Lond.). British. 38, Wood Lane, Isleworth, Middlesex. Student, Acton Technical College. *Signed by:* W. Davey, J. H. Skellon, E. G. Cowley.

Bok, Louis Dennis Corydon, M.Sc. (Stellenbosch), Dr.rer.Nat. (Leipzig). South African. 16, Vicarage Gardens, Campden Hill, W.8. Senior Lecturer at the University of Natal. *Signed by:* A. Briscoe, A. A. Eldridge, F. C. Tompkins.

Born, Renate Ursula, B.Sc. (Glas.), A.R.I.C. British. 1, Wallingford Avenue, London, W.10. Chemist, J. Lyons & Co. *Signed by:* E. B. Hughes, R. W. Money, J. H. Bushill.

Brocklehurst, Brian. British. Fair View, Gobowen, Oswestry, Shropshire. Student at Oxford University. *Signed by:* Harry Irving, E. J. Bowen, L. E. Sutton.

Brook, Adrian Gibbs, B.A. and Ph.D. (Toronto). Canadian. Department of Organic Chemistry, Imperial College of Science and Technology, South Kensington, S.W.7. Nuffield Research Fellow in Organic Chemistry. *Signed by:* R. P. Linstead, E. H. Braude, J. E. H. Hancock.

Brown, Frederick. British. Nancyville, Shincliffe Village, Co. Durham. Research Student. *Signed by:* G. H. Christie, John E. Gregory, W. K. R. Musgrave.

***Buist, Gabriel John,** B.Sc. (Lond.). British. 30, Barrow Point Avenue, Pinner, Middlesex. Research Student. *Signed by:* C. A. Bunton, G. J. Bullen, E. A. Halevi.

Casy, Alan Frederick, B.Sc. (Lond.), Ph.C. British. 68, Boileau Road, Barnes, S.W. 13. Part-time teacher at Chelsea Polytechnic. *Signed by:* A. H. Beckett, Douglas C. Harrod, L. Saunders.

***Child, Peter John.** British. 2, Baxter Road, Islington, N.1. Junior Assistant Chemist, Spratts Patent, Ltd., London, E.14. *Signed by:* H. Holness, M. A. Crook, F. C. Hymas.

Clark, Donald John, M.Sc. (Melbourne). Australian. Glenwood, Bakeham Lane, Virginia Water, Surrey. Research at Royal Holloway College. *Signed by:* A. Graham Foster, Gwyn Williams, K. Singer.

Colonna, Martino, D.Chem. (Pavia). Italian. Istituto Chimico, Universita Degli Studi, Trieste. Professor of Organic Chemistry. *Signed by:* C. K. Ingold, C. A. Bunton, J. G. Ross.

Cresswell, William Thomas, B.Sc. (Birm.), A.R.I.C. British. 71, Hillcrest Road, Bromley, Kent. Lecturer, Woolwich Polytechnic. *Signed by:* G. H. Jeffery, A. I. Vogel, J. Leicester.

Daniels, David George Herbert, M.A. (Cantab.). British. 12, Lemsford Road, St. Albans, Herts. Organic Chemist, Cereals Research Station. *Signed by:* J. K. Whitehead, D. J. Cosgrove, B. Shaw.

***Dimond, Edwin Richard,** B.Sc. (Lond.). British. 17, Armfield Road, Enfield, Middlesex. Student. *Signed by:* M. R. Porter, G. Mattock, R. A. Tingey.

***Dyer, Maurice John,** B.A. (Oxon.). British. 104, Conway Road, Newport, Mon. Student. *Signed by:* Harry Irving, F. M. Brewer, S. G. P. Plant.

***Eason, Albert Barfield.** British. 46, Francis Street, Waterloo Road, Wolverhampton, Staffs. Chemist, The Goodyear Tyre and Rubber Co. (G.B.), Ltd., Wolverhampton. *Signed by:* A. Turner, D. C. Wall, D. A. Higgins.

Ellis, John Frederick, B.Sc. (Dunelm). British. 14, The Square, Sedgefield, Nr. Stockton-on-Tees, Co. Durham. Research Student. *Signed by:* John Gregory, G. H. Christie, W. K. R. Musgrave.

***Ferguson, Ian.** British. 230, Cairnhill Circus, Glasgow, S.W.2. Student. *Signed by:* J. S. McLean, N. R. Fisk, P. G. Dunley.

Flegg, Peter Beaumont, B.Sc. (Reading). British. Mushroom Research Station, Yaxley, Peterborough, Northants. Research Chemist. *Signed by:* R. L. Edwards, Cyril Tyler, G. Tinsley.

***Freeman, Peter Charles.** British. 45, Pretoria Road, Leytonstone, E.11. Laboratory Assistant, North Thames Gas Board, London, E.6. *Signed by:* L. W. Blundell, D. G. Murdoch, C. A. Ray.

***Gadsby, Brian.** British. 27, Parkhill Road, Chingford, E.4. Student. *Signed by:* R. A. Tingey, H. Holness, G. Mattock.

***Genge, John Arthur René.** British. 19, Forty Acres Ground, Canterbury, Kent. Student at University College, Southampton. *Signed by:* K. R. Webb, E. Cartmell, N. B. Chapman.

Green, Joseph, B.Sc. and Ph.D. (Lond.), A.R.I.C. British. 24, St. Albans Avenue, London, W.4. Research Chemist. *Signed by:* P. R. Watt, R. L. Collett, A. F. Daglish.

***Griffiths, Peter John Felix,** B.Sc. (Wales), A.R.I.C. British. 72, Maindy Road, Cathays, Cardiff. Research Student. *Signed by:* S. T. Bowden, N. M. Cullinane, A. J. C. Wilson.

Halfpenny, Arthur Clare, B.Sc. (Lond.). British. 48, Holly Terrace, Hensingham, Whitehaven, Cumberland. Director, Marchon Products, Ltd. *Signed by:* Albert Taylor, Harry Gregson, A. W. Doyle.

***Harden, Gerald Douglas,** B.Sc. (Lond.). British. 18, Heythorp Street, Southfields, London, S.W. 18. Student. *Signed by:* C. K. Ingold, E. D. Hughes, G. J. Bullen.

Harrison, John Marcus, A.R.I.C. British. W. Walker & Sons, Ltd., Rose Hill Tannery, Bolton, Lancs. Chief Chemist. *Signed by:* D. Burton, J. P. Danby, D. Cyril Griffiths.

***Harrison, James Lumner,** B.Sc. (Lond.), A.R.I.C. British. Quorn Hall, Loughborough, Leics. Research Student, Loughborough College. *Signed by:* R. F. Phillips, J. M. Connolly, G. O. G. Oldham.

***Hastings, Garth Winton.** British. Brooklyn, Coatham Mundeville, Nr. Darlington, Co. Durham. Student, University of Birmingham. *Signed by:* L. L. Bircumshaw, James C. Robb, W. Wilson.

***Heggs, Thomas Geoffrey,** B.Sc. (Leeds), A.R.I.C. British. 6, Luther Street, Rodley, Leeds, Yorks. Research Student. *Signed by:* P. A. Briscoe, W. A. Wightman, J. W. Baker.

***Holmes, Jack Anthony.** British. 30, Old Farleigh Road, Selsdon, Surrey. Student at King's College, London. *Signed by:* S. H. Harper, A. J. B. Robertson, E. K. Rideal.

Hooper, Kenneth Charles, B.Sc. (Lond.), A.R.C.S. British. 27, Minster Road, Lonond, N.W.2. Research Student, Royal College of Science. *Signed by:* H. N. Rydon, P. W. G. Smith, H. E. Khaden.

***Howard, George Eric,** B.Sc. (Lond.), A.R.I.C. British. 27, Telferscot Road, Balham, S.W.12. Research Student. *Signed by:* E. E. Turner, J. W. Smith, D. M. Hall.

Hughes, Beaumont Percy, B.Sc. (Reading). British. Ford House, Henly Road, Wargrave, Berks. Research Student. *Signed by:* Paul F. Holt, D. T. King, J. Bowcott.

Humphrey-Smith, Cecil Raymond. British. 9, Nevill Way, Hove 4, Sussex. Research Chemist. *Signed by:* N. H. Pritt, G. E. Watts, T. J. Morrison.

Innes, Kenneth Keith, A.B. (Central, Mo.), Sc.M. (Brown U.), Ph.D. (Washington). American. Division of Physics, National Research Council, Ottawa, Ontario, Canada. Research Fellow. *Signed by:* D. W. Davidson, P. J. Dyne, A. D. E. Pullin.

Islam, Ahmad Medhat, M.Sc. (Fouad Ist Univ.). Egyptian. 38, Lansdowne Crescent, Glasgow, N.W. Research Student. *Signed by:* James D. Loudon, P. A. Ongley, Ralph A. Raphael.

***Jones, Peter Marshall.** British. 16, Stratford Way, Watford, Herts. Student at London University. *Signed by:* A. M. James, W. A. Ross, J. F. J. Dippy.

Keller, Richard Thomas, S.B. (Wisconsin). American. Chemistry Department, Box 68, The University, Mississippi, U.S.A. Instructor. *Signed by:* A. L. Wilds, William S. Johnson, S. M. McElvaine.

***Kraychy, Stephen,** B.Sc. (Alberta). Canadian. Department of Chemistry, University of Wisconsin. Madison 6, Wisconsin, U.S.A. Graduate Student. *Signed by:* A. L. Wilds, S. M. McElvaine, W. S. Johnson.

***Learmouth, Ivan Archibald,** B.Sc. (Lond.). British. 42, Wilton Crescent, Shirley, Southampton. Research Student at University College, Southampton. *Signed by:* A. R. Burkin, E. Cartmell, K. R. Webb.

***Lee, Michael John Wells.** British. Resthaven, Ashwell, Nr. Baldock, Herts. Student. *Signed by:* Brenda M. Prestt, N. Macleod, L. Hunter.

Liff, Dennis, B.Sc. (Lond.). British. 78, Hartington Court, Lansdowne Way, London, S.W.8. Industrial Chemist. *Signed by:* F. R. Goss, N. P. H. Brown, E. W. Hood.

Mangini, Angelo, D.Chem. (Rome). Italian. Istituto Chimica Industriale Universita, Viale Risorgimento 22, Bologna, Italy. Professor of Industrial Organic Chemistry. *Signed by:* C. K. Ingold, D. P. Craig, E. D. Hughes.

***McConnell, John Denholm McKendrick,** B.Sc. (Glas.), A.R.I.C. British. 81, Bath Street, Abingdon, Berks. Scientific Officer, A.E.R.E., Harwell. *Signed by:* J. S. Anderson, J. Sutton, B. G. Roberts.

***Michael, Dennis Gordon,** B.Sc. (Lond.), A.R.I.C. British. 53, Hurstwood Road, Temple Fortune, London, N.W.11. Chemist. *Signed by:* J. H. Bushill, M. A. Brooks, G. E. Forstner.

***Mills, John Stuart,** B.Sc. (Lond.), A.R.C.S. British. 84, Wodeland Avenue, Guildford, Surrey. Research Chemist, National Gallery, Trafalgar Square. *Signed by:* A. E. Werner, H. J. Plenderleith, W. A. Akers.

***Mortoza, Ahmed,** B.Sc. (Dacca). Pakistani. c/o Educational Attaché, Office of the High Commissioner for Pakistan in U.K., Education Dept., 39, Lowndes Square, London, S.W.1. Special Trainee for Govt. of Pakistan at Woolwich Arsenal. *Signed by:* S. A. Butt, H. K. Suttle, R. F. Phillips.

Mulholland, Daniel Booth, M.Sc. and Ph.D. (Q.U.B.), A.R.I.C. British. c/o Givaudan & Co., Ltd., Godstone Road, Whyteleafe, Surrey. Technical Director. *Signed by:* J. Bell, W. H. D. Morgan, I. F. B. Smyth.

***North, Alan Arthur,** B.Sc. (Lond.), A.R.I.C. British. 22, Mayfield Drive, Loughborough, Leics. Research Student. *Signed by:* I. R. F. Phillips, G. Oldham, J. M. Connolly.

Oppenheim, Gerald Frederick, B.Sc. (Melbourne). Australian. 41, Linden Gardens, London, W.2. Chemist at J. Lyons & Co., W.14. *Signed by* L. H. Lampitt, G. E. Forstner, F. J. Griffin.

Paterson, Colin, B.Sc. (Lond.), F.R.I.C. British. Standards Works, Southwark Street, London, S.E.1. Director at Stevenson & Howell, Ltd. *Signed by:* E. B. Hughes, C. A. Bassett, J. H. Bushill.

***Raper, Alan Humphrey,** B.Sc. (Leeds). British. Devonshire Hall, Cumberland Road, Leeds 6. Research Student at Leeds University. *Signed by:* P. A. Briscoe, J. W. Baker, W. A. Wightman.

Raum, Alaric Louis Jeffrey, B.Sc. (Lond.). British. 17, Poulett Gardens, Twickenham, Middlesex. Research Chemist, The Distillers Company, I td., Epsom. *Signed by:* S. H. Harper, D. H. Hey, D. W. G. Style.

***Ridgwell, Stanley Arthur,** B.Sc. (Lond.). 15, Sandringham Drive, Welling, Kent. Research Student. *Signed by:* E. E. Turner, J. W. Smith, G. R. Hilldrith.

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PAPERS RECEIVED

(List of papers received between October 17th and November 13th, 1951.)

"The possibility of geometrical isomerism in diazoaminobenzene." By H. C. FREEMAN and R. J. W. LE FÈVRE.

"Poly(vinyl thiol) and related compounds. Part I. The oxidation of poly(vinylsulphonic acid) with aqueous hydrogen peroxide solutions." By H. T. HOOKWAY and B. SELTON.

"The synthesis of neurotropic and musculotropic stimulators and inhibitors. Part V. Derivatives of aminophenyl phosphates as anticholinesterases." By K. J. M. ANDREWS, F. R. ATHERTON, F. BERGEL, and A. L. MORRISON.

"The stability of poly(vinyl acetate) in technical mustard-gas solution." By J. IDRIS JONES.

"The 2 : 3-4 : 5-dimethylene acetals of allitol and talitol." By S. A. BARKER and E. J. BOURNE.

"Amino-acids and peptides. Part VII. The autohydrolysis of glutamyl-peptides." By W. J. LE QUESNE and G. T. YOUNG.

"The sorption of vapours by ferric oxide gel. Part III. Aliphatic amines." By MARJORIE J. BROWN and A. GRAHAM FOSTER.

"Tropolones. Part IV. The preparation of αβ-benzotropolone." By J. W. COOK, A. R. M. GIBB, R. A. RAPHAEL, and A. R. SOMERVILLE.

"Colchicine and related compounds. Part XII. Some molecular rearrangements." By J. W. COOK, J. JACK, and J. D. LOUDON.

"Andrographolide. Part I." By (MRS.) D. CHAKRAVARTI and R. N. CHAKRAVARTI.

"The reaction of diazonium salts with furylacrylic acid. Part I." By WALTER FREUND.

"A new synthesis of arsonic acids. Part II. Coupling of αβ-unsaturated carbonyl compounds with diazotised *p*-arsanilic acid and 4-amino-2-nitrophenylarsonic acid." By WALTER FREUND.

"A new synthesis of arsonic acids. Part III. Coupling of furan, β-furylacrylic acid, thiophen, and β-thienylacrylic acid with *p*-arsanilic acid." By WALTER FREUND.

"The estimation of water in pyridine homologues by the use of infra-red spectroscopy." By E. A. COULSON, J. L. HALES, and E. F. G. HERINGTON.

"The preparation of *p*-dimethylaminoacetophenone and homologues." By A. W. NINEHAM.

"Action of Grignard solutions. Part IV. Action of Grignard solutions on (*a*) substituted derivatives of naphthasultone, (*b*) *N*-phenyl-*o*-benzoic sulphinide and *N*-phenylbenz*iso*thiazolone, and (*c*) *pseudo*saccharin chloride." By AHMED MUSTAFA and MUSTAFA KAMAL HILMY.

"Reactions with benzoxanthrones." By AHMED MUSTAFA and MUSTAFA KAMAL HILMY.

"The isolation of L-stachydrine from the fruit of *Capparis tomentosa*." By J. W. CORNFORTH and ALAN J. HENRY.

"The presence of *cis*- and *trans*-3-hydroxystachydrine in the fruit of *Courbonia virgata*." By J. W. CORNFORTH and ALAN J. HENRY.

"On the chemical kinetics of autosynthetic systems." By SIR CYRIL HINSHELWOOD.

"Losses of (radioactive) sulphur and phosphorus from resting bacterial cells." By T. C. N. CARROLL, C. J. DANBY, A. C. R. DEAN, and SIR CYRIL HINSHELWOOD.

"The molecular structure of pyrrole and some of its simple derivatives, from electric dipole moment measurements." By HELMER KOFOD, L. E. SUTTON, and (in part) J. JACKSON.

"Chemistry of lichens and fungi. Part I. Polyporic acid in stictæ." By J. MURRAY.

"New syntheses of heterocyclic compounds. Part XVI. Some further observations on ring closures involving loss of nitrous acid." By S. S. BERG and V. PETROW.

"The photochemical decomposition of keten in light of very high intensity." By K. KNOX, R. G. W. NORRISH, and G. PORTER.

"Synthetic long-chain aliphatic compounds. Part VII. Some mono-olefinic acids." By (MISS) B. W. BOUGHTON, R. E. BOWMAN, and (in part) D. E. AMES.

"Synthetic long-chain aliphatic compounds. Part VIII. The preparation of *cis*- and *trans*-undec-9-enoic acids." By D. E. AMES and R. E. BOWMAN.

"Synthetic long-chain aliphatic compounds. Part IX. Some anti-tuberculous long-chain amines." By D. E. AMES and R. E. BOWMAN.

"Absorption spectra of substances containing the carbon–iodine bond. Part II." By T. M. DUNN and T. IREDALE.

"Cyclic polymerisation of acetylene. Examination of the $C_{10}H_{10}$ fraction." By D. S. WITHEY.

" Investigations on aromatic sulphides and sulphones. Ultra-violet absorption of some diaryl sulphides." By A. MANGINI and R. PASSERINI.

" The absorption spectrum of allene in the far ultra-violet." By L. H. SUTCLIFFE and A. D. WALSH.

" Action of acrylonitrile on ethyl aminomalonate and ethyl aminoacetate." By WESLEY COCKER, B. E. CROSS, and (MISS) JOAN MCCORMICK.

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" The structure of dihydrophenylthebaine." By K. W. BENTLEY and SIR ROBERT ROBINSON.

" The reduction of thebaine and dihydrothebaine by sodium and ammonia." By K. W. BENTLEY, SIR ROBERT ROBINSON, and A. E. WAIN.

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" The kinetics of halogen addition to unsaturated compounds. Part XXII. Alkyl- and halogenoalkyl-ethylenes." By P. W. Robertson, J. K. Heyes, and B. E. Swedlund.

" The polymerizability of methyl 1-*tert.*-butylacrylate." By J. W. C. Crawford and (Miss) S. D. Swift.

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INSTITUTE OF PHYSICS. Vacuum physics. A symposium held . . . 27 and 28 June, 1950. London 1951. pp. iii + 80. ill. (Supplement No. 1, *Journal of Scientific Instruments*.) (*Reference*.) From the Institute.

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PENNSYLVANIA STATE COLLEGE. *Phi Lambda Upsilon*, and *Departments of Chemistry and Chemical Engineering*. A symposium on developments in applied chemistry. State College, Pennsylvania 1951. [various pp.] (25th Annual Priestley Lecture.) (*Reference*.) From the Bureau of Abstracts.

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UNITED STATES. *Department of Commerce. National Bureau of Standards*. Circular 508. Reference table for thermocouples. By HENRY SHENKER, JOHN I. LAURITZEN, JR. and ROBERT J. CORRUCCINI. Washington, D.C. 1951. pp. [ii] + 71. (*Reference*.)

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